

## Adverse drug reaction profiles of commonly used platinum compounds in cancer chemotherapy

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### ABSTRACT

**Background:** The aim of the present study was to monitor and analyze the pattern of occurrence of adverse drug reactions (ADRs) to commonly used platinum compounds in MNJ Cancer Hospital, Hyderabad.

**Methods:** Cancer patients, who received platinum compounds as chemotherapy regimen, were monitored for adverse reactions. Cancer patients belonging to either gender and of all ages, who were receiving platinum compounds under any standard regimen, were included for the study. Cases that were unlikely, conditional or unaccessible under World Health Organization (WHO)-Uppsala Monitoring Centre causality criteria were excluded from the study. The ADRs were recorded in Central Drugs Standard Control Organization forms. Causality was assessed by the WHO Causality Assessment Scale and Naranjo's Algorithm. Preventability and severity of ADRs were assessed by modified Schumock and Thornton scale, modified Hartwig and Siegel scale, respectively.

**Results:** Among 100 patients, 78 developed ADRs to platinum compounds. The reactions observed were vomiting, diarrhea, abnormal renal function tests, myelosuppression, anemia, thrombocytopenia, alopecia, and constipation. The WHO Causality Assessment Scale indicated 64.6% "possible" and 35.4% "probably," but no "certain" reactions. Naranjo's Algorithm showed 59.4% "possible" 40.6% "probable" reactions. 48% reactions were "definitely preventable" 16% were "probably preventable" and 36% were "not preventable." Modified Hartwig and Siegel Scale of severity assessment showed that 12% reactions were "mild" 69% were "moderate" and 19% were severe.

**Conclusion:** Platinum compounds have 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.

**Keywords:** Adverse drug reactions, Platinum compounds, Cancer, Chemotherapy

### INTRODUCTION

Adverse drug reaction (ADR) is defined as any noxious or unintended response to a drug, which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.<sup>1</sup> ADRs are a major cause of morbidity, hospital admission, increased healthcare expenditure, and even death.<sup>2</sup> In most instances, ADRs are of relatively mild intensity and disappear when the drug is discontinued or the dose is changed. In nearly 5% of therapeutic drug courses, however, ADRs complicate medical treatment and require admission to a hospital.<sup>3</sup> In a meta-analysis of 39 prospective studies from hospitals in the United States, it was even estimated that more than 100,000 deaths can be attributed annually to serious ADRs and it was concluded that ADRs rank from the

fourth to sixth leading cause of death.<sup>4</sup> A more recent study in England ascertained the current burden of ADRs through a prospective analysis of all hospital admissions.<sup>5</sup> It could be shown that at any time the equivalent of up to seven 800 bed hospitals may be occupied by patients admitted with ADRs.<sup>5</sup> Besides the impact on the individual's health status, ADRs thus impose a high financial burden on the healthcare system. Some countries spend up to 15-20% of their hospital budget dealing with drug complications<sup>6</sup> with high costs also in the ambulatory setting.<sup>7</sup> These direct costs should be added to the indirect costs such as loss of productivity. Hence, with the increase in production of various pharmaceutical products, newer drugs are being introduced every year and hence there is need for an active surveillance system to remove the harmful drugs that have entered the market was well-realized by the World Health Organization (WHO). This has

been the basis for starting the International Drug Monitoring Program by the WHO.

Among cancer chemotherapeutic agents platinum compounds have broad antineoplastic activity and have become the foundation for treatment of ovarian, head and neck, bladder, esophagus, lung, and colon cancers and they have high potential for toxicity especially for cisplatin.<sup>8</sup> In one study conducted in inpatients of internal medicine wards at a tertiary care hospital, Gujarat, most of the fatal and life-threatening reactions occurred due to chemotherapeutic agents and majority of patients discontinued suspected drug and recovered from ADRs.<sup>9</sup> In another study conducted in a tertiary care teaching hospital in Eastern India, cisplatin was responsible for 29% of the total ADRs. The ADRs associated with the use of cisplatin are nausea, vomiting, myelosuppression, peripheral neuropathy, ototoxicity, and nephrotoxicity. Elderly patients are at higher risk of myelosuppression, nephrotoxicity, and neurotoxicity due to cisplatin. Cyclophosphamide, 5-fluoro uracil, paclitaxel, and adriamycin were found to be other important drugs to cause ADRs. Cisplatin and these four drugs were very commonly used for the treatment of cancer. Hence, they resulted in the development of the maximum number of ADRs.<sup>10</sup>

In a study conducted in India among 51 patients, 48 developed ADRs to cisplatin-based chemotherapy. The reactions observed were nausea, alopecia, anorexia, vomiting, taste alteration, diarrhea, constipation, tinnitus, and hypocalcemia.<sup>11</sup> In one study titled "Pattern of ADRs due to cancer chemotherapy in Tertiary care Teaching Hospital in Gujarat", platinum compounds (54.29%), antimetabolites (48.71%), and taxanes (29.52%) were mostly responsible for ADRs.<sup>12</sup>

However, the number of ADR reports from the cancer wards to the pharmacovigilance center was minimal in our hospital. The reason for this paradox was not clear. It could be either due to gross underreporting of ADRs or due to effective preventive measures being adopted for the patients receiving cancer chemotherapy. As platinum compounds are one of the most commonly used drugs for cancer chemotherapy, so there is need to monitor and analyze the pattern of ADRs due to platinum compounds in cancer chemotherapy.

## **METHODS**

This prospective, observational study was carried out in the department of radiotherapy, MNJ Cancer Hospital, Hyderabad for the duration of 6 months. The Institutional Ethics Committee approval was obtained prior to initiation of the study.

### ***Inclusion criteria***

Cancer patients belonging to either gender and of all ages, who were receiving platinum compounds under any standard

regimen, were included for the study. The patients received cancer chemotherapy as per the assessment of the treating physician. No changes in the treatment decision, schedule or duration were made as part of the study.

### ***Exclusion criteria***

Cases that were unlikely, conditional or unassessable under WHO-Uppsala Monitoring Centre causality criteria<sup>13</sup> were excluded from the study.

Clinical and treatment data were collected from the inpatient case records. All routine investigations like complete blood picture, serum electrolytes, renal function tests were done before administering each cycle of platinum compounds and the treatment was given only when these investigations were normal. Adequate pretreatment with parenteral dexamethasone, ranitidine, and ondansetron was given to all patients. Potassium chloride and magnesium sulfate were given to patients on cisplatin-based chemotherapy regimen.

Monitoring for adverse effects was done based on daily questioning of symptoms during their admission period in hospital. To record ADRs, Central Drugs Standard Control Organization forms were used. Causality was assessed by both WHO Causality Assessment Scale<sup>13</sup> and Naranjo's Algorithm.<sup>14</sup> Preventability was assessed by Modified Schumock and Thornton scale.<sup>15</sup> The severity of ADRs was assessed by modified Hartwig and Siegel scale.<sup>16</sup>

The WHO Causality Assessment Scale is recommended by the WHO Uppsala Monitoring Center, which is the WHO collaborating center for International drug monitoring, for evaluation of the causal relationship of drugs to its adverse drug effects.

The Naranjo's Algorithm, a questionnaire designed by Naranjo et al. consists of objective questions with three types of response – yes, no or do not know. Scores are given accordingly and the drug reaction can be classified as definite, probable or possible.

The Modified Schumock and Thornton scale classifies ADRs as definitely preventable, probably preventable, and not preventable based on a set of questions for each level.

The Modified Hartwig and Siegel scale classifies severity of ADR as mild, moderate or severe with various levels according to factors like requirement for change in treatment, duration of hospital stay, and the disability produced by the ADR.

No invasive investigation was undertaken or suggested to the treating physician as a part of the study. The drug effects which were described by the patients and effects which were diagnosed and reported by the physician were documented.

## RESULTS

At the end of study period, a total of 100 patients who received platinum compounds as chemotherapy regimen were monitored for adverse reactions during their hospital admission period. Among them, 75 patients received cisplatin, 16 patients received carboplatin, 9 patients received oxaliplatin. This included 58 female patients and 42 male patients. The various indications were carcinoma cervix, carcinoma ovary, carcinoma colon, lung cancer, head and neck cancer, carcinoma stomach, carcinoma esophagus, osteosarcoma. The most common indication was carcinoma cervix.

Among the 100 patients observed 78 developed adverse reactions to the chemotherapy regimen. This includes 43 female patients and 35 male patients. Total of 96 ADRs noted among 78 patients. This included 33 patients received cisplatin alone and others with one additional anticancer drug (paclitaxel, etoposide, 5-fluorouracil, gemcitabine, epirubicin, ifosfamide, adriamycin, topotecan with cisplatin; paclitaxel, etoposide with carboplatin; 5-fluorouracil, capecitabine with oxaliplatin) and 6 patients with two additional anticancer drugs (bleomycin, etoposide, with cisplatin; epirubicin, capecitabine with cisplatin). Twenty patients who developed ADRs received concomitant radiotherapy.

The ADRs observed in the patients were vomiting, diarrhea, alopecia, constipation, myelosuppression, abnormal renal function tests, anemia, thrombocytopenia (Table 1 and Figure 1). Vomiting was the most common ADR. Tinnitus, tingling and numbness, seizures were encountered in each one patient. The prevalence of ADRs mostly occurred in the age group between 41 and 50 years (Figure 2).

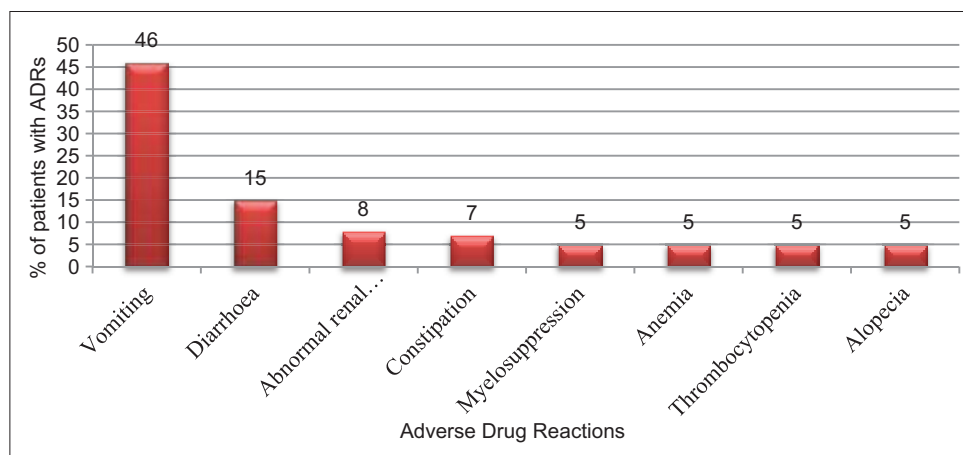
Assessment of causality by WHO Causality Assessment Scale<sup>13</sup> indicated that 62(64.6%) reactions belong to the category “possible,” followed by the category “probable” with frequency of 34 (35.4%) (Table 2). There were no “certain” reactions as rechallenge was not attempted in any

of the patients. However, the grade of causality for each ADR remained low due to the presence of co-administered drugs. As per Naranjo’s Algorithm<sup>14</sup> 57 (59.4%) ADRs were categorized as “possible” with score ranging from 1 to 4 and 39 (40.6%) of the ADRs were categorized as “probable” with score ranging from 5 to 8 (Table 3). Assessment of preventability of the ADR was done based on modified Schumock and Thornton scale.<sup>15</sup> It shows 46 (47.9%) ADRs were “definitely preventable,” 15 (15.6%) ADRs were “probably preventable” and 35 (36.5%) ADRs were “not preventable” (Figure 3). Based on modified Hartwig and Siegel scale<sup>16</sup> of severity assessment, 12 (12.5%) ADRs were of less severity categorized as “mild,” 66 (68.75%) ADRs were categorized as “moderate” and 18(18.75%) ADRs were categorized as “severe” (Figure 4).

## DISCUSSION

Platinum compounds are the most commonly used antineoplastic agents. Some of the well-documented ADRs of these drugs include nausea, vomiting, renal toxicity, ototoxicity, peripheral neuropathy, hypersensitivity reactions and electrolyte disturbances, myelosuppression.<sup>17</sup> Most of the ADRs documented in this study comprised one or more of these reactions. Although an adequate premedication with parenteral dexamethasone, ranitidine and ondansetron were given to each patient, the frequency of vomiting remained high due to high emetogenic potential of these drugs. The study has demonstrated the need to improve the management of vomiting, since the rates of prevention of these expected adverse effects of these drugs were poor.

Nausea and vomiting are very common side effects of cancer chemotherapeutic agents.<sup>18</sup> These drugs may induce vomiting by both a central action on the chemoreceptor trigger zone (CTZ) and a peripheral action on the gastrointestinal tract. The dominant receptors in the CTZ located in the floor of the fourth ventricle are serotonin Type 3 and dopamine Type 2.<sup>19</sup> As serotonin receptors in the brain are involved in the mechanism of acute onset vomiting, ondansetron has a definite role in its prevention.<sup>20</sup>



**Figure 1: Frequency of adverse drug reactions to platinum compounds.**

**Table 1: Various ADRs caused by platinum compounds.**

ADRs	Cisplatin	Carboplatin	Oxaliplatin	Total
Vomiting	37	6	3	46
Diarrhea	13	2	-	15
Abnormal renal function tests	5	1	2	8
Constipation	5	2	-	7
Myelosuppression	1	3	1	5
Anemia	-	4	1	5
Thrombocytopenia	1	3	1	5
Alopecia	-	3	2	5
Total	62	24	10	96

ADRs: Adverse drug reactions

**Table 2: Causality assessment of individual ADR by WHO Causality Assessment Scale.**

ADRs	Number of ADRs				Total
	Certain	Probable	Possible	Unlikely	
Vomiting	-	25	21	-	46
Diarrhea	-	3	12	-	15
Abnormal renal function tests	-	5	3	-	8
Constipation	-	-	7	-	7
Myelosuppression	-	-	5	-	5
Anemia	-	1	4	-	5
Thrombocytopenia	-	-	5	-	5
Alopecia	-	-	5	-	5
Total (%)	-	34 (35.4)	62 (64.6)	-	96

ADRs: Adverse drug reactions, WHO: World Health Organization

**Table 3: Causality assessment of individual ADR by Naranjo's Algorithm.**

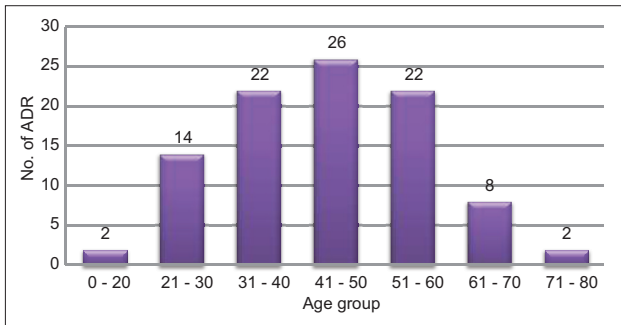
ADRs	Number of ADRs			Total
	Possible	Probable	Definite	
Vomiting	18	28	-	46
Diarrhea	11	4	-	5
Abnormal renal function tests	2	6	-	8
Constipation	7	-	-	7
Myelosuppression	5	-	-	5
Anemia	4	1	-	5
Thrombocytopenia	5	-	-	5
Alopecia	5	-	-	5
Total (%)	57 (59.4)	39 (40.6)	-	96

ADRs: Adverse drug reactions

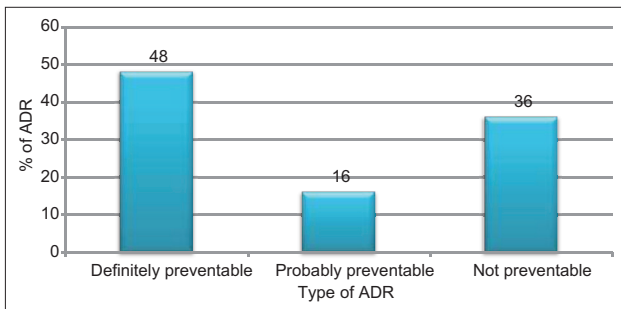
Next common adverse effect was diarrhea. Diarrhea can occur due to mucosal cell toxicity. Animal studies have demonstrated the effect of cisplatin causing specific mitochondrial oxidative DNA damage in gastrointestinal mucosal cells and increased gastrointestinal permeability, an indicator of toxicity.<sup>21</sup>

Renal function tests were abnormal in eight patients. Nephrotoxicity is a well-established adverse effect of cisplatin, may be dose-limiting, and can manifest as

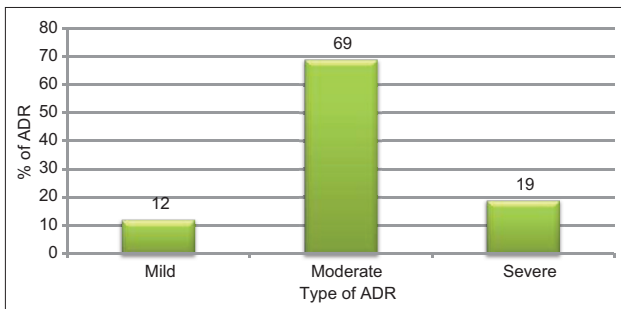
acute or chronic renal failure, polyuria, or a chronic hypomagnesemia. The mechanism appears to involve primarily damage to the proximal renal tubule; selective magnesium loss may be due to a specific membrane or transport system abnormality. Sulfhydryl metabolism and oxidative stress play a role in toxicity.<sup>22</sup> Adequate hydration and chloride diuresis may prevent cisplatin-induced nephrotoxicity. Amifostine is a thiophosphate cytoprotective agent that reduces renal toxicity associated with repeated administration of cisplatin, but is not



**Figure 2: Prevalence of adverse drug reaction in different age group.**



**Figure 3: Preventability assessment of adverse drug reaction by Modified Shumock and Thornton scale.**



**Figure 4: Severity assessment of adverse drug reaction by Modified Hartwig and Siegel scale.**

commonly used.<sup>17</sup> Carboplatin, oxaliplatin also causes nephrotoxicity.

Myelosuppression was seen in five patients. Anemia and thrombocytopenia were seen in each five patients. Cisplatin causes mild to moderate myelosuppression with transient leukopenia and thrombocytopenia. Anemia may become prominent after multiple cycles of treatment. The dose-limiting toxicity of carboplatin is myelosuppression, primarily thrombocytopenia. Hematological toxicity is mild to moderate for oxaliplatin, except for rare immune-mediated cytopenias.<sup>17</sup> Neutropenia can be managed by sargramostim (granulocyte-macrophage colony-stimulating factor), filgrastim (granulocyte-colony-stimulating factor). Thrombocytopenia requires oprelvekin (recombinant human IL-11) or platelet transfusion. Anemia due to chemotherapy can be managed by erythropoietin, hematinics, and blood transfusion.<sup>23</sup>

Ototoxicity can be more severe in children. It can manifest as tinnitus and loss of hearing in the high-frequency range.<sup>24</sup> In the present study, only one tinnitus case was reported.

Electrolyte imbalances such as hypomagnesemia, hyponatremia, hypocalcemia, hypokalemia are known to occur.<sup>17</sup> There were no cases of electrolyte imbalances in the present study as pretreatment with parenteral magnesium sulfate and potassium chloride were given to each patient. Hypocalcemia and hyponatremia were not observed in the present study.

A study by Surendiran et al., on ADR profile of cisplatin-based chemotherapy 41% patients developed vomiting, 23% developed diarrhea, 51% developed alopecia, 10% developed tinnitus and there were no hematological abnormalities.<sup>11</sup> In the present study, 49% developed vomiting, 17% developed diarrhea, only one patient developed tinnitus, and there was one case of myelosuppression and one case of thrombocytopenia and no one developed alopecia due to cisplatin-based chemotherapy regimen.

In the present study, there were no “certain” drug reactions as the patients were not subjected to rechallenge of the drug. Most common ADR was vomiting so 48% of ADRs were preventable and remaining 36% ADRs were not preventable due to the poor predictability of the ADRs and poorly understood mechanisms to explain their cause. Most of the reactions were of less severity, and there would be no strong indication to change or withhold the drug for milder adverse effects.

There is a need for effective pharmacovigilance in India owing to the absence of Indian data on adverse effects and the genetic diversity of the Indian population.

## CONCLUSION

Platinum compounds have a high potential to cause various adverse effects in cancer patients. Most common adverse effect was vomiting. Vomiting can be preventable, so there is the need to improve the management of vomiting, since the rates of prevention of these adverse effects were poor.

Other adverse effects like alopecia, peripheral neuropathy, hypersensitivity reactions are not predictable. Renal toxicity and myelosuppression are more common in elderly and ototoxicity is more common in children. Adequate hydration and chloride diuresis can prevent renal toxicity.

Anemia can be managed by erythropoietin, hematinics, and blood transfusion. Thrombocytopenia requires oprelvekin (Recombinant human IL-11) or platelet transfusion. Neutropenia can be managed by sargramostim (Granulocyte-Macrophage Colony stimulating factor), filgrastim (Granulocyte Colony-stimulating factor).<sup>23</sup>

In the present study, causality of adverse effects was poor due to the presence of co-administered drugs. This study also emphasizes the need to improve pharmacovigilance awareness among physicians in order to improve the pharmacovigilance in India.

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