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Research Article

Adverse drug reaction profile of cisplatin-based chemotherapy regimen in a tertiary care hospital in India

M. B. Sasmi*

Department of Pharmacology, Government Medical College, Thiruvananthapuram, Kerala, India

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*Correspondence to:
Dr. M. B. Sasmi,
Email: sasmianuraj@gmail.com

ABSTRACT

Background: This study was undertaken to analyze the pattern of occurrence of adverse drug reaction (ADR) to cisplatin-based chemotherapy regimen in an oncology ward of a tertiary care hospital.

Methods: Cancer patients who received cisplatin-based chemotherapy were monitored for ADRs. The collected reports were analyzed for demographic and drug details; causality, preventability, and severity of ADRs. Causality assessed by the WHO Causality Assessment Scale and Naranjo's Algorithm. Preventability and severity assessed by Schumock–Thornton scale and modified Hartwig–Siegel scale, respectively.

Results: Among 138 patients, 125 developed adverse reactions to cisplatin-based chemotherapy. The results observed were alopecia, nausea, vomiting, renal toxicity, peripheral neuropathy, electrolyte imbalance, etc. The WHO Assessment Scale showed 95% possible and 5% probable reactions. Whereas Naranjo's Algorithm showed 83% probable and 17% possible reactions. Most of the reactions belonged to the category of "not preventable." Reactions such as nausea and vomiting belonged to the category of "definitively preventable." Modified Hartwig–Siegel scale showed most of the reactions were of mild Level 1 category.

Conclusions: Cisplatin-based regimen has high potential to cause adverse effects. Most of the reactions were mild in nature, but not preventable. The common adverse effects, such as nausea and vomiting, were preventable.

Keywords: Causality, Chemotherapy, Cisplatin, Pharmacovigilance

INTRODUCTION

Adverse drug reaction (ADR) encompasses any new signs and symptoms other than the desired effect of a drug which occurs at therapeutic doses. ADRs constitute a major clinical problem in terms of human suffering and increased healthcare costs. Lazarou et al. have highlighted the public health importance of ADR in hospital.[1]

Pharmacovigilance deals with detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems. Pharmacovigilance and reporting of ADRs are important because the information collected during the pre-marketing phase of drug development is inevitably incomplete with regard to rare ADRs. The National Pharmacovigilance Program in India was started with the objectives of monitoring the safety of drugs and creation of ADR database for the Indian population.[2] The major effects of pharmacovigilance are early detection of unknown adverse reactions, detection of increase in frequency of known adverse reactions, identification of risk factors and dissemination of information.[3]

Among the patients of oncology, ADRs of cancer treatments have become almost synonymous with the treatment itself. The low therapeutic index of chemotherapeutic agents and the predictable and common adverse events of cancer treatments mean that these events are seen as unavoidable components of treatments. A recent study from a South Indian tertiary care teaching hospital has reported anti-neoplastic agents as the common class of drugs causing the ADRs accounting for a total of 21.8% of the reported ADRs.[4] In a study conducted in Nepal, about the pattern of ADRs due to cancer chemotherapy, it was reported that cisplatin was the individual drug responsible for 44% of the ADRs.[5]

Cisplatin is a potent anti-neoplastic agent with associated toxicities, but because of its broad anti-neoplastic activity, cisplatin forms the foundation of most chemotherapy regimens of head and neck tumors, metastatic testicular

tumors carcinoma breast, esophagus, urinary bladder, ovary and lung.[6] In a recent study on ADR profile of cisplatin-based chemotherapy by Surendiran et al.[7] in the south Indian population, 94% of the patients developed ADRs to cisplatin chemotherapy with nausea and alopecia being the most common ADRs.

Considering the impact of ADRs on morbidity and mortality rates and the immense potentiality of cancer chemotherapeutic agents to produce a wide range of ADRs, especially cisplatin, studies to evaluate the incidence and nature of ADRs in the population are warranted. Therefore, this study was taken up with a motive to monitor and determine the frequency, severity, and preventability of ADRs due to cisplatin-based chemotherapeutic regimens.

METHODS

This was a prospective observational study, conducted in the Department of Radiotherapy and Oncology in our tertiary care hospital over a period of 3-month. ADR data were collected as per WHO definition. Ethical clearance was obtained from the Institutional Human Ethics Committee prior to the study. Confidentiality and anonymity of the patient's information were maintained during and after the study.

Inpatients and outpatients of either sex who received cisplatin-based chemotherapy regimen were included in the study. Those patients who did not receive cisplatin as a part of the drug regimen were excluded from the study. A written informed consent was obtained from the patient/guardian/relative. All the relevant information regarding the patient were obtained and recorded in the preformed proforma. Inpatients were evaluated daily for the presence of ADRs and were observed until their discharge from the hospital. Outpatients were followed up for next two visits. The monitoring was done based on daily questioning for symptoms and monitoring of routine laboratory investigation reports. When a suspected ADR was reported, data on that particular suspected reaction were collected and documented in a suitably designed ADR documentation form. All the relevant data including information regarding drugs the patient had received before the onset of the reaction, their respective dosages, and their routes of administration with frequency, laboratory data results present in the medical records, clinical details, and treatments were recorded. No invasive investigation was undertaken 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.

The collected data were analyzed for demographic details, drug details, causality, preventability, and severity of adverse effects. Causality (evaluation of the causal relationship of drugs to its adverse effects) was assessed by both WHO Causality Assessment Scale[8] and Naranjo's Algorithm.[9] The

WHO scale assess the causality based on some preformed description of the adverse reactions. According to that ADRs were classified into certain, probable, possible, unlikely, unclassified, and unclassifiable. The Naranjo's Algorithm is a questionnaire which consists of objective questions with three types of responses - Yes, no or do not know. Scores were given accordingly, and the reaction was classified as definite, probable, or possible. The preventability of ADRs was assessed by Schumock and Thornton scale.[10] This scale classified ADRs as definitely preventable, probably preventable, and not preventable based on a set of questions for each level. The severity of ADRs was assessed by modified Hartwig and Siegel scale.[11] The severity of ADR was classified as mild, moderate, or severe with various levels according to factors such as requirement for change in treatment, duration of hospital stay, and disability produced by adverse reactions.

RESULTS

Prospective evaluation of 138 patients who were receiving cisplatin-based regimens in the oncology ward was carried out, and the data were analyzed. The age range of study population was 12-84 years. Mean age of the patients was 54.48 years. Number of cases with ADRs were maximum (33.3%) in the age interval of 50-59 years. The majority of patients were males (61%). The various indications for cisplatin-based regimens were carcinoma lung, cervix, breast, ovary, oral cavity, esophagus, stomach, urinary bladder, etc. (Figure 1). The most common indication was lung cancer (26%) followed by oral carcinoma cavity (10.9%) and carcinoma ovary (10.1%).

All the patients received hydration therapy, including 500 ml 0.9% saline (NS), 500 ml dextrose normal saline, 100 ml mannitol as intravenous infusions, 30 minutes before cisplatin. All the 138 patients (100%) received ranitidine 50 mg and 136 patients (98.6%) received dexamethasone 8 mg as intravenous injections. 136 patients (98.6%) received antiemetics, either ondansetron 8 mg (16.9%) or
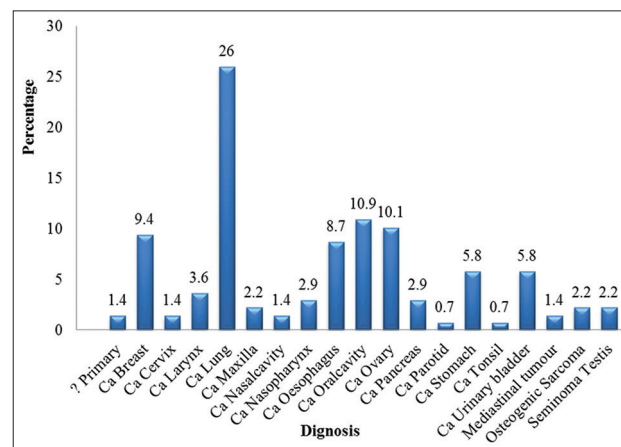
Figure 1: Indications of cisplatin-based regimens in the study population.

granisetron 3 mg (16.9%) or palanosetron 0.25 mg (12.5%) as intravenous injection.

Among the 138 patients observed, 125 patients (90.6%) developed adverse reactions to chemotherapy regimens (Figure 2). Among the patients who developed ADR, 40.6% had only one ADR and 50% had more than one ADR. 13 patients (9.4%) did not develop ADRs to cisplatin chemotherapy. Among the 125 patients who developed ADR, 7 patients (5.6%) received cisplatin alone, 103 patients (82.4%) received cisplatin with one additional cytotoxic drug, 13 patients (10.4%) received cisplatin with two additional cytotoxic drugs, and 2 patients (1.6%) received cisplatin with three additional cytotoxic drugs. The additional cytotoxic drugs used were 5-fluorouracil, gemcitabine, etoposide, docetaxel, paclitaxel, vinblastine, adriamycin, methotrexate, cyclophosphamide, etc. The most common combination regimen was cisplatin – 5-fluorouracil.

The ADRs observed in the patients were nausea, vomiting, anorexia, constipation, alopecia, anemia, neutropenia, elevated creatinine, arthralgia, etc. (Figure 3). Alopecia (42.8%) was the most frequent adverse reaction among this study population. It was followed by nausea (26.8%) and vomiting (24.6%). A total of 237 ADR cases were evaluated. Causality of individual ADR was assessed by WHO

Causality Assessment Scale showed that 95.4% (226 ADRs) of the reactions belong to the category "possible," followed by category "probable," which includes 4.6% (11 ADRs) of reactions. There were no certain/unlikely/unclassified/unclassifiable reactions (Table 1). Causality of individual ADR was also assessed by Naranjo's Algorithm. 82.7% (196 ADRs) of the reactions were categorized as "probable" with a score ranging from 5 to 8 and 17.3% (41 ADRs) of the reactions categorized as "possible" with a score ranging from 1 to 4. There were no "definite" reactions (Table 2).

Assessment of preventability of ADRs was done based on Modified Schumock and Thornton Scale. Most of the ADRs belonged to the category "not preventable." Nausea and vomiting came under the category "definitely preventable" and constipation came under "probably preventable" category. Assessment of severity of individual ADRs was done by Modified Hartwig and Siegel Scale. Most of the ADRs (94.5%) were of less severity categorized as "mild Level 1" severity. 5.5% of the ADRs categorized as "moderate Level 3" severity, which include some cases vomiting and anemia.

DISCUSSION

ADRs constitute a major clinical problem and are a significant public health concern. Cancer chemotherapy is a section which contributes a major part of the drug-related reactions. Cisplatin is one of the most commonly used drugs among the cancer chemotherapeutic agent.

In the present study, the majority of the patients belong to the age group of 50-59 years (33.3%) with male predominance (61%), which was similar with the study done by Mallik et al.[5] But, female predominance (66.7%) was observed in the study by Surendiran et al.[7] The most common indication for cisplatin-based regimen in the present study was carcinoma lung (26%) followed by carcinoma oral cavity. In a similar Indian study, it was seen that carcinoma cervix was the most common indication for cisplatin-based regimen followed by carcinoma lung.[7] This difference could be due to the male predominance in the present study, whereas the other study showed female predominance.

Among the 138 patients observed, 125 patients (90.6%) developed an adverse reaction to the chemotherapy regimen. This included 7 patients (5.6%) receiving cisplatin alone, 103 patients receiving cisplatin along with one additional anticancer agent. Only 13 patients did not develop ADRs to cisplatin chemotherapy. The most common combination used was cisplatin - 5-fluorouracil. In a similar study done in South India, 94.2% of the patients developed ADR to the chemotherapy regimen, but in contrast to the present study more than half of the patients (52.1%) who developed ADR were receiving cisplatin alone.[7]

Some of the well-documented ADRs of this drug include nausea, vomiting, renal toxicity, ototoxicity, peripheral
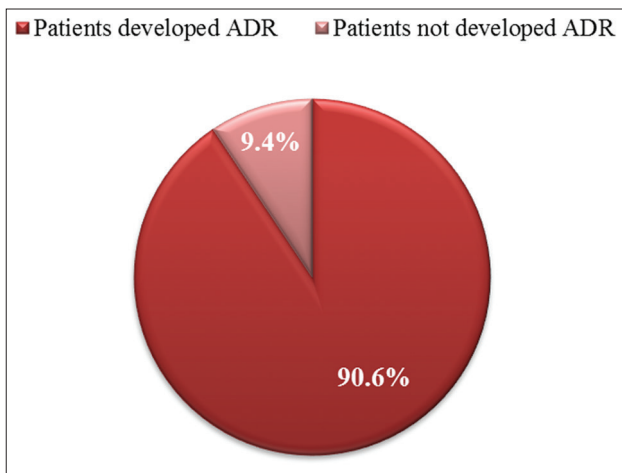

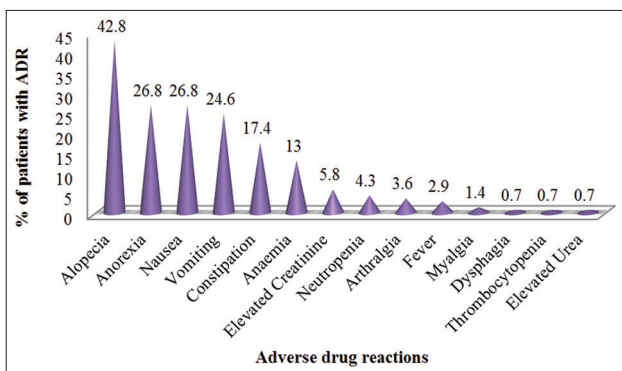**Figure 2: Incidence of adverse drug reaction.**

Figure 3: Prevalence of adverse drug reaction among the study population.

Table 1: Causality assessment of individual ADR by WHO causality assessment scale.

ADRs	Number of ADRs				Total
	Certain	Probable	Possible	Unlikely	
Alopecia	-	4	55	-	59
Anorexia	-	-	37	-	37
Nausea	-	1	36	-	37
Vomiting	-	3	31	-	34
Constipation	-	1	23	-	24
Anaemia	-	1	17	-	18
Elevated creatinine	-	1	7	-	8
Neutropenia	-	-	6	-	6
Arthralgia	-	-	5	-	5
Fever	-	-	4	-	4
Myalgia	-	-	2	-	2
Dysphagia	-	-	1	-	1
Thrombocytopenia	-	-	1	-	1
Elevated urea	-	-	1	-	1
Total	-	11	226	-	237

ADR: Adverse drug reaction

Table 2: Causality assessment of individual ADR by Naranjo's Algorithm.

ADRs	Number of ADRs			Total
	Possible*	Probable*	Definite*	
Alopecia	-	59	-	59
Anorexia	16	21	-	37
Nausea	10	27	-	37
Vomiting	4	30	-	34
Constipation	-	24	-	24
Anaemia	2	16	-	18
Elevated creatinine	-	8	-	8
Neutropenia	1	5	-	6
Arthralgia	-	5	-	5
Fever	4	-	-	4
Myalgia	2	-	-	2
Dysphagia	1	-	-	1
Thrombocytopenia	1	-	-	1
Elevated urea	-	1	-	1
Total	41	196	-	237

ADR: Adverse drug reaction

neuropathy, hypersensitivity reactions, and electrolyte disturbances. The most frequent adverse reactions reported in this study were alopecia (42.8%), anorexia (26.8%), nausea (26.8%), and vomiting (24.6%). Most common hematological abnormality documented was anemia (13%). Some of the rarer reactions include myalgia, arthralgia, thrombocytopenia, and elevated urea levels. In a similar study by Surendiran et al., it was found that 54.9% and 41.2% of the patients developed nausea and vomiting, respectively, which is higher than the present study. Studies by Bahl et al.[12] and by Chen et al.[13] on patients with lung cancer, treated with cisplatin-based chemotherapy, also reported the slightly higher frequency of nausea and vomiting. This difference could be attributed to adequate pre-medications. Almost all patients received parenteral dexamethasone, ranitidine, and $5HT_3$ antagonists such as ondansetron/granisetron/palanosetron before cisplatin administration. Even after all these pre-medication mild nausea and vomiting was still present and this was due to the high emetogenic potential of cisplatin.

42.8% of the patients developed alopecia which was less in the present study when compared with other studies.[7,12,14]

Earlier studies have shown conflicting results implicating cisplatin as a common causative agent for alopecia as well as an unlikely agent for alopecia.[12,15,16] In our study, out of 59 patients who developed alopecia, only 5 patients were on monotherapy with cisplatin and the remaining patients had concurrent cytotoxic drugs along with cisplatin. The occurrence of anorexia was also slightly less in the present study compared with other studies.[7,12] The frequency of constipation in the present study was 17.4%, and it is almost consistent with findings of the studies by Zucali et al.[17] and by Surendiran et al.[7] Though the study by Surendiran et al.[7] reported diarrhea as an adverse reaction, the present study did not observe such effect. The hematological disturbances documented in the present study was lower, compared to other studies.[12,13,17,18] However, the frequency of anemia was almost similar with the study by Zucali et al.[17] The study by Surendiran et al.,[7] did not report any hematological disturbances. The frequency of increased levels of serum creatinine reported in this study was less than that observed in other previous studies.[12,19] This difference could be due mandatory hydration to all patients who received cisplatin. The difference in the frequency of ADRs could be related to the difference in the methodology used to detect ADRs, the sample size and the classes of drugs used.

In the present study, causality assessment was done with WHO Causality Assessment Scale and Naranjo's Algorithm. Almost all the ADRs (95%) are assessed as "possible" with a lower level of causality by WHO scale (Table 1). This could be due to the presence of other co-administered anticancer drugs. The rest were assessed as "probable." There were no "certain" reactions as the patients were not subjected to re-challenge of the drug. But, most of the ADRs (83%) except fever, myalgia, arthralgia, and thrombocytopenia assessed as "probable" with a high level of causality based on Naranjo's Algorithm (Table 2). This shows more objective nature of Naranjo's Algorithm. This disagreement between the results of causality assessment could be related to the difference in the causality assessment definition and questionnaires.[20] The results of the present study were consistent with the findings in the similar study by Surendiran et al.[7] In the study by Jose and Rao[4] about the ADR pattern in a tertiary care hospital, they rated more than 50% of the ADRs as "probable," on causality assessment by Naranjo's Algorithm.

The current study showed that most of the ADRs were not preventable, and this may be due to the poor predictability of ADRs and poorly understood mechanisms to explain their cause. It also reported that the common ADRs, such as nausea and vomiting, were definitely preventable and therefore with adequate pre-medications these reactions can be effectively controlled. These findings were similar to the study by Surendiran et al.[7] They reported constipation as definitely preventable, whereas in this study it was reported as probably preventable. This difference could be related to frequent prescription of stool softeners to the patients in this institution. All the ADRs were assessed for their severity, and this study reported the majority of the ADRs were of mild severity as observed in the previous study.[7] There would be no strong indication to change or withhold the drug for milder adverse effects. Thus, this study had carried out a focused ADR monitoring on cisplatin-based chemotherapy for cancer patients.

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