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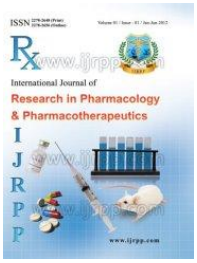

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Pattern of adverse drug reactions of cisplatin based drug regimen in a tertiary care cancer institute

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ABSTRACT

Aims

To assess the pattern of adverse drug reactions in patients receiving cisplatin based cancer chemotherapy in tertiary care cancer institute.

Materials and Methods

A prospective, observational study was carried out from February 2014 to march 2015 after getting an approval from human ethical committee. Clinical and treatment data were collected from patients who underwent cisplatin based chemotherapy during the study period. Central Drugs Standard Control Organization (CDSCO) forms was used to record the adverse drug reactions (ADRs). The ADRs were assessed for causality, severity, preventability and predictability by suitable scales.

Result

During the study period, a total of 163 ADRs were reported from 54 patients received cisplatin based chemotherapy. Out of them 23(42.59%) were males and 31(57.41%) were females. Prevalence of oral cancer (44.4%) and cervical cancer (20.37%) were higher. Most of ADRs were associated with gastrointestinal system (57.83%).Vomiting 39(72.2%) was most frequent ADR reported. Other ADRs observed were nausea, alopecia, diarrhea, bone marrow depression, constipation, numbness, mucositis.

Conclusion

Cisplatin is one of the most widely used anticancer drug and has a high potential to cause various adverse effects in cancer patients. Gastrointestinal ADRs were much more frequent than others. Most of the reactions were probably preventable with use of premedication.

Keywords: Cisplatin, Adverse drug reactions (ADRs), Central Drugs Standard Control Organization (CDSCO).

INTRODUCTION

Adverse drug reactions (ADRs) are a global problems constitute a major clinical problem in terms of human suffering adding economic burden to the society. Sometimes the ADRs are so serious and severe that, cost needed to treat morbidity and mortality due to it, is more than the cost needed to treat the actual condition of interest {1}. According to WHO an Adverse Drug Reaction (ADR) is defined as "a response to a drug which is noxious & unintended, which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function excluding failure to accomplish the intended

purpose {2}. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems {3}. Pharmacovigilance is the ongoing process to monitor drug safety and to make available new information and knowledge about ADRs for early detection of unknown adverse reactions, increase in frequency of known adverse reactions, identification of risk factors and dissemination of information {4}. Safety data generated from clinical trials is incapable of identifying infrequent or late-onset adverse drug reactions {5}. Hence, the need for an active surveillance system to remove the harmful drugs that have entered the market was well realized by the WHO. This has been the basis for starting the International Drug Monitoring Program by the WHO {6}.

Chemotherapeutic drugs have a narrow therapeutic index and the dosage needed to achieve a therapeutic response usually proves toxic to the body's rapidly proliferating cells like bone marrow, gastrointestinal tract and hair follicles. Some agents have other organ specific toxicities. Additionally, some drugs are associated with immediate adverse reactions which are a result of their biochemical nature rather than their action against tumors. Use of cancer chemotherapeutic drugs is associated with several adverse effects (AE) ranging from mild nausea to fatal myelosuppression {8}. The side effects of cancer chemotherapy agents may be acute, self-limited, and mild or can be chronic, permanent, and potentially life threatening in nature.

The safety profile study of cisplatin based cancer chemotherapy is not carried out in our hospital till yet, so we decided to conduct this type of study in the cancer ward of a cancer institute.

MATERIALS AND METHODS

A prospective, observational, spontaneous reporting study approved by the Institutional Ethics Committee (IEC) was conducted from February, 2014 to march, 2015 among inpatients of oncology ward at J K cancer institute, GSVM medical college Kanpur. Cancer patients belonging to either gender and of all ages, who were receiving cisplatin based cancer chemotherapy under any standard regimen, were included for the study. The suspected ADR reporting form recommended by central drugs standard control organization (CDSCO) was used for collection of all the relevant information regarding the patient.

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 a part of the study. No invasive investigation was undertaken or suggested to the treating physician by the investigator as a part of the study.

The patients admitted for cancer chemotherapy and receiving cisplatin as the part of regimen were monitored for adverse effects till their discharge from hospital. 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. Active surveillance was done by reviewing the medical records, drug charts, laboratory results and interviewing the cancer patients in order to find the adverse drug reactions. The drug effects which were described by the patients and effects which were diagnosed and reported by the physician were documented.

The collected reports were analyzed for causality, severity, preventability and predictability by suitable scales. Causality was assessed by WHO causality assessment scale recommended by the WHO Uppsala Monitoring Center and were categorized as certain, probable, possible, unlikely, unclassified as well as unclassifiable {9}. Preventability was assessed by modified Schumock and Thornton scale classifies ADRs as definitely preventable, probably preventable and not preventable based on a set of questions for each level {10}. The severity of ADRs was assessed by 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 adverse drug reaction {11}.

RESULTS

During the study period, a total of 163 ADRs were reported from 54 patients received cisplatin based chemotherapy. In our study population, 31 (57.4%) were females, 23 (42.6%) were males (Figure 1). The age of the patients ranged from 15 to 75 years and the median age was 46 year. Majority of patients were in the age group of 41 to 60 years 26 (48.14%), followed by 20 (37%) in the age group of 21 to 40 years (Figure 2). Cisplatin based regimen prescribed for various malignancies among most prevalent were carcinoma oral cavity 23(42.6%), cervix 11(20.37%), ovary 4(7.4%),

larynx 3(5.55%), sarcoma 3(5.55%), esophagus 2(3.7%), lungs 2(3.7%), ear 2(3.7%).

Among the 54 patients who developed ADR, 16(29.63%) patients received cisplatin alone, 25(46.3%) received cisplatin along with one additional anti cancer drug, 12(22.2%) received with two additional anti cancer drug, only single patient received with three additional anti cancer drug. The additional anti cancer drug used were Fluorouracil, Paclitaxel, Adriamycin, Cyclophosphamide, Ifosfamide, Gemcitabine, Etoposide, Bleomycin, Docetaxel, etc. The most common combination chemotherapy regimen received was cisplatin - 5fluorouracil (31.5%) (Table 1).

Among 163 ADRs reported majority of them associated with cisplatin - 5fluorouracil combination 53 (32.5%) followed by cisplatin alone 43 (26.4%).The ADRs observed in the patients were vomiting, alopecia, myelosuppression, nausea, taste alteration, constipation, diarrhea, anorexia, mucositis, numbness, black pigmentation, dysuria, arthralgia, etc. Among vomiting (72.2%) was the most common ADR followed by alopecia (33.3%), myelosuppression (27.8%) and nausea (25.9%), taste alteration (24%).

WHO causality assessment scale showed that 130(79.75%) of the reactions belong to the category "possible," followed by category "certain," which includes 23(14.11%) of reactions (Figure 3). Assessment of preventability of ADRs was done based on Modified Schumock and Thornton Scale showed Most of the ADRs belonged to the category "not preventable" (55.21%). ADRs such as Nausea, vomiting, constipation came under the category "probably preventable" (44.78%) (Figure 4). Modified Hartwig's severity scale showed that most of the reactions were of mild category (51%) followed by moderate (49%) category. No reactions found to be severe (Figure 5).

Table 1: Frequency of various cisplatin based drug regimen with patients and ADRs

S.N.	Drug regimen	Number of patients (%) (N=54)	No. of ADRs reported (%) (n=163)
1	Cisplatin	16 (29.63)	43 (26.38)
2	Cisplatin +Fluorouracil	17 (31.48)	53 (32.51)
3	Cisplatin+ Paclitaxel	3 (5.55)	12 (7.36)
4	Cisplatin+ Cyclophosphamide	2 (3.7)	10 (6.13)
5	Cisplatin +Adriamycin	2 (3.7)	2 (1.23)
6	Cisplatin+ Gemcitabine	1 (1.85)	2 (1.23)
7	Cisplatin+Etoposide +Bleomycin	2 (3.7)	5 (3.07)
8	Cisplatin+Docetaxel +Fluorouracil	3 (5.55)	8 (4.9)
9	Cisplatin+Paclitaxel +Fluorouracil	5 (9.26)	21 (12.88)
10	Cisplatin+Adriamycin+Ifosfamide	2 (3.7)	4 (2.45)
11	Cisplatin+Ifosfamide+ Adriamycin+Vincristine	1 (1.85)	3 (1.84)

Table 2: Frequency of ADRs due to cisplatin based drug regimen

S.N.	ADRs observed	Number of ADRs reported	Percentage (%)
1	Vomiting	39	72.22
2	Alopecia	18	33.33
3	Myelosuppression	15	27.78
4	Nausea	14	25.92
5	Taste alteration	13	24.07
6	Constipation	11	20.37
7	Diarrhea	9	16.67
8	Anorexia	7	12.96
9	Mucositis	5	9.26
10	Numbness	4	7.41
11	Fever	3	5.55
12	Anxiety	3	5.55
13	Black pigmentation	2	3.7
14	Dysuria	2	3.7

15	Decrease hearing	1	1.85
16	Others	17	31.48

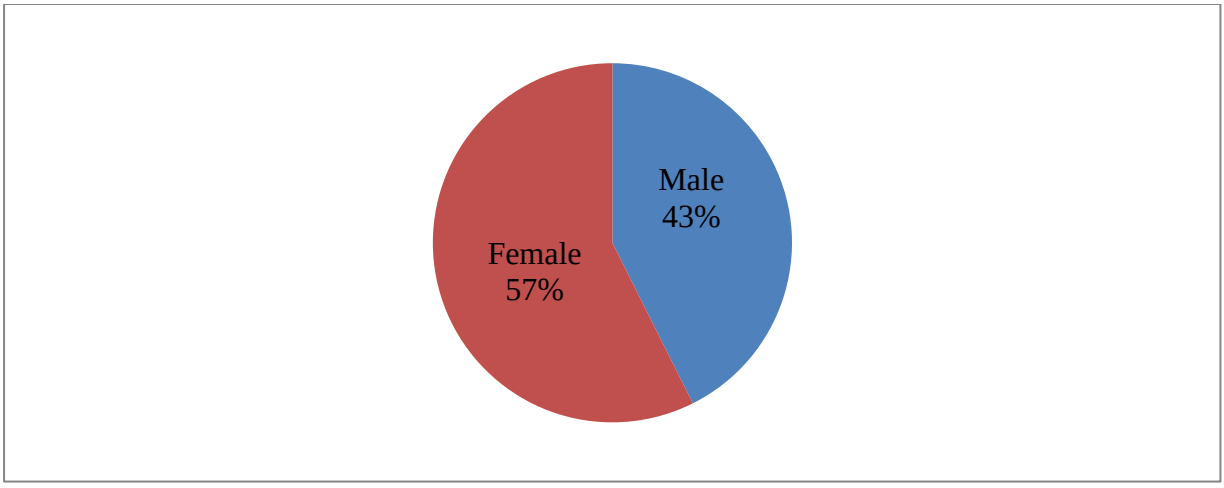

Figure 1: Sex distribution of study population

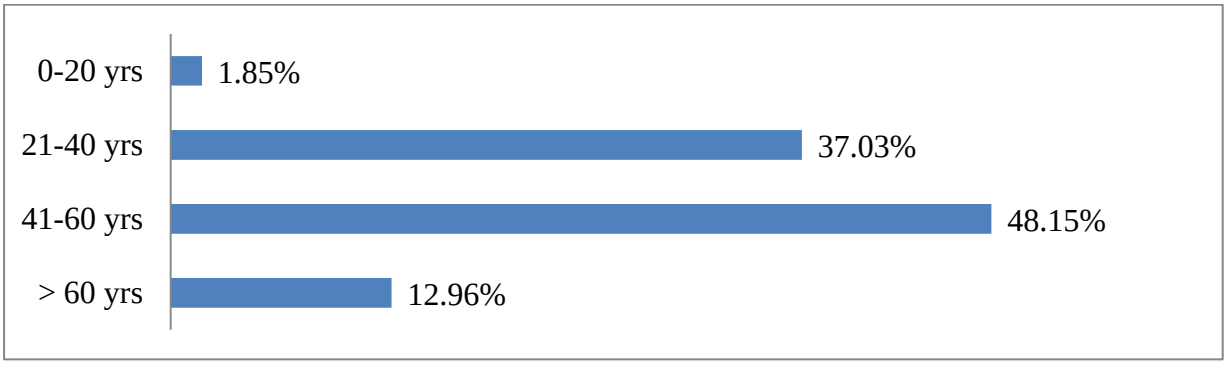

Figure 2: Age distribution of study population

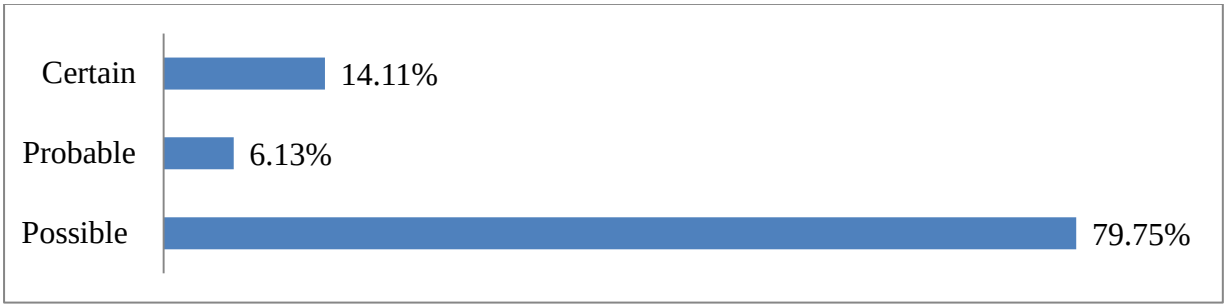

Figure 3: Causality assessment as per WHO Causality Assessment Scale

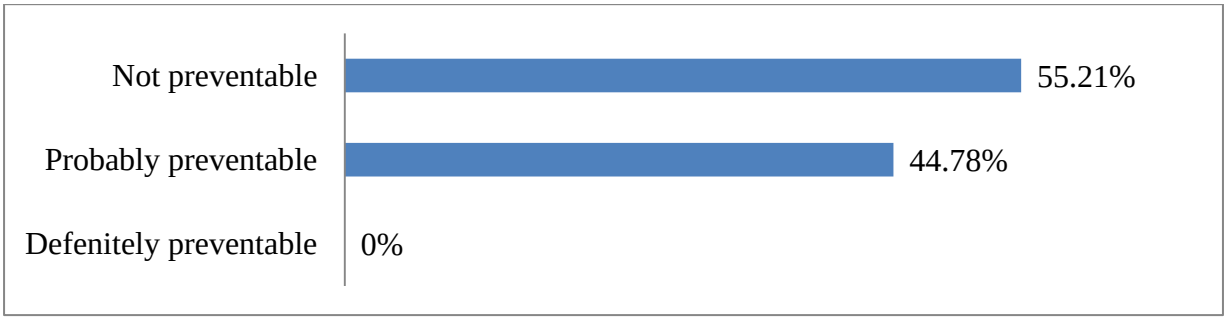

Figure 4: Preventability assessment as per Modified Schumock and Thornton Scale

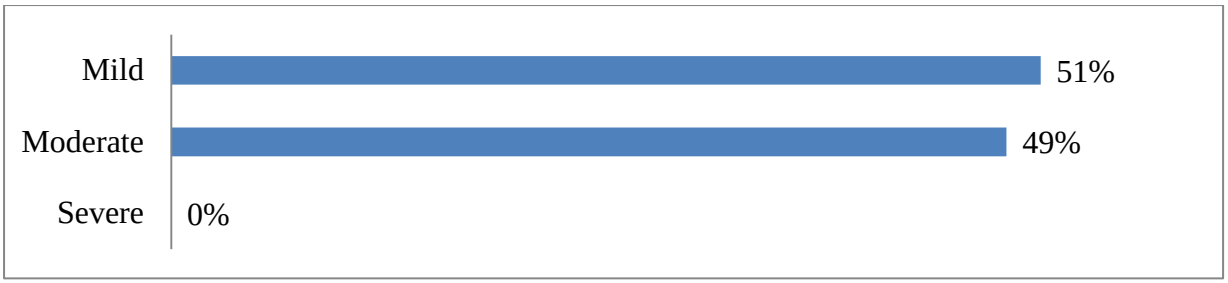

Figure 5: Severity assessment as per Modified Hartwig's severity scale

DISCUSSION

Anticancer drugs have very high tendency to produce ADRs because they are designed to be cytotoxic and thus often injure normal cells in addition to the malignant cells. This damage to normal cells causes side effects.

Cisplatin is one of the most commonly used anticancer drugs. In our study numbers of female patients (57.4%) were higher than male (42.6%) producing ADRs. female predominance (66.7%) was also observed in the study by Surendiran et al [{12}]. In our study the prevalence of ADRs was most common in the age group between 41-60 years (26%). This finding is in similar with study conducted by Poddar et al [{13}]. This may be due to the low metabolizing capacity and reduced excretory functions leading to accumulation of drugs in the body and thus increasing the risk of ADRs. As a result extra precautions should be taken while using chemotherapy in the elderly population. The most common indication for cisplatin-based drug regimen was carcinoma oral cavity 23(42.6%), followed by cervix 11(20.37%), ovary 4(7.4%).

In our study among 54 patients who developed ADR, (29.63%) patients received cisplatin alone and the most common combination chemotherapy regimen received was cisplatin - 5fluorouracil (31.5%). Majority of ADRs caused by cisplatin based chemotherapy found to be associated with cisplatin - 5fluorouracil combination (32.5%), however a similar study conducted by Surendiran et al showed more than half of the patients (52.1%) who developed ADR were receiving cisplatin alone. Anticancer drugs were mostly prescribed in combination in current study. This finding is consistent with the existing utilization pattern of anticancer drugs (Mayer and Janoff, 2007).

The most frequent ADRs reported in our study were vomiting (72.2%) followed by alopecia (33.3%), myelosuppression (27.8%) and nausea (25.9%). Most common hematological abnormality documented was neutropenia (9.26%). This is In contrast with study of M. B. Sasmi in which the most frequent ADRs reported were alopecia (42.8%), anorexia (26.8%), nausea (26.8%), and vomiting (24.6%) and most common hematological abnormality documented was anemia (13%) [{14}].

A similar study conducted by Surendiran et al, showed that 54.9% and 41.2% of the patients developed nausea and vomiting, respectively. Study by Bahl et al [{15}], on patients with lung cancer, treated with cisplatin in combination with etoposide, also reported Nausea and vomiting were the most common non -hematological and Anemia was the most common hematological toxicity observed (81%) in contrast to neutropenia (9.26%) in our study. The frequency of alopecia was reported (88%) as compared to (33.3%) in our study.

Nausea and vomiting are prominent ADRs of cisplatin and with most cytotoxic agents and is caused mainly due to direct stimulation of chemoreceptor trigger zone (CTZ). Among patients who developed vomiting (64%) were on combination chemotherapy. Almost all patients received adequate pre-medication with parenteral dexamethasone, ranitidine, and 5HT3 antagonists such as ondansetron before cisplatin administration, nausea and vomiting was still present due to the high emetogenic potential of cisplatin.

Alopecia (33.3%) was the next most common ADR reported slightly less in our study compared to (51%) in Surendiran et al, and (42.8%) in M. B. Sasmi study. Among patients who developed Alopecia (94.4%) were on combination chemotherapy.

The ADR prevalence encountered suggest that practically all patients receiving cytotoxic drugs suffer one or more ADRs. The spectrum of drugs encountered is typical of a medical oncology unit subjecting patients to various combination chemotherapy regimens. However, the percentage figures indicating involvement of individual drugs in adverse events has to be interpreted with caution

since it may simply be dependent on the frequency of usage of the drug. Thus, cisplatin being the most frequently incriminated drug does not necessarily mean that it is the one most prone to cause ADRs; it may reflect the fact that cisplatin is one of the most widely used anticancer drugs in that unit.

In the present study, causality assessment was done with WHO Causality Assessment Scale. Most of the ADRs (79.75%) were 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 current study showed that most of the ADRs (55.21%) were not preventable, and this may be due to the poor predictability of ADRs and poorly understood mechanisms to explain their cause. ADRs such as Nausea, vomiting, constipation came under the category "probably preventable" (44.78%) as with adequate pre-medication they can be well controlled. Most of the reactions were of mild category (51%) followed by moderate (49%) category. No reaction found to be severe. There would be no strong indication to change or withhold the drug for milder adverse effects.

A major limitation of our study is that we analyzed only 163 ADRs (small sample size) and this did not cover all the patients receiving chemotherapy during the study period. Since it was a observational study, there are chances of under-reporting and incomplete documentation of data regarding ADRs in the case records.

CONCLUSION

Cisplatin is one of the most widely used anticancer drugs and has a high potential to cause various ADRs in cancer patients. Most of the ADRs were mild in severity but not preventable so there was no need to change in treatment. Majority of ADRs were associated with gastrointestinal system. Combination drug regimen induces more ADRs compared to monotherapy. 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.

There is a great need to set up an effective ADR monitoring and reporting system in cancer hospitals and also to create awareness among health care professionals working in tertiary care cancer hospitals regarding the importance of this system. Most of the ADRs in hospitalized oncology patients are predictable and at least probably preventable. Rational and judicious use of preventive measures will lead to a reduction in the incidence and severity of ADRs and thereby unpleasant suffering in already mentally and physically bothered human being and reduce economic burden to the cancer patient and society.

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