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Short Communication

IDENTIFICATION AND ANALYSIS OF ADVERSE DRUG REACTIONS ASSOCIATED WITH CANCER CHEMOTHERAPY IN HOSPITALIZED PATIENTS

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ABSTRACT

Objective: To analyze the incidence of adverse drug reactions (ADRs) associated with chemotherapeutic drugs and study its management.

Methods: A prospective observational study was carried out on hospitalized patients undergoing cancer chemotherapy. The identified ADRs were assessed for causality, severity and preventability.

Results: Among 120 patients followed 100 patients developed 161 ADRs. Most common ADRs were anemia, leucopenia, mucositis fever, and chills. As per the WHO causality assessment 87(54.0%) ADRs were probable whereas with the Naranjo's scale 98(60.9%) were probable. Moderate reactions were 59.62%. Majority 122 (75.8%) of the ADRs were not preventable. Most of ADRs were implicated with cisplatin followed by 5-Fluro-uracil and the combination drugs which included FAC (Flurouracil, adriyamycin, cyclophosphamide) regimen, Paclitaxel, and Carboplatin (PC) regimen.

Conclusion: Patients undergoing cancer chemotherapy have higher chances to develop ADRs. Those patients on chemotherapy with cisplatin followed by 5-Fu and combination drugs which include FAC and PC regimen should be strictly monitored for the early detection and prompt management of the ADR to prevent morbidity and mortality.

Keywords: Adverse drug reactions, Cancer, Chemotherapy, Predictable, Management.

Drugs are widely used because of their ability to effect the biological systems of the body. The use of these drugs may also carry certain unwanted or unintended effects. Each time a patient is exposed to a drug we cannot be certain about the unwanted effects of the product. However, we can learn from previous experience where patients have been exposed to the similar drug. ADR is recognized as a hazard of drug therapy. It may develop promptly or only after prolonged medication or even after stoppage of the suspected drug. The World Health Organization defines an ADR as "any reaction that is noxious and unintended and occurs at a dose normally used in man for diagnosis, prophylaxis and treatment of diseases or for modification of physiological function"[1].

Cancer has become a global burden because of the aging, increased adoption of cancer-causing behaviors particularly smoking and exposure to triggering factors like chemicals, radiations, unhealthy eating habits and a sedentary lifestyle. Different modalities for treatment of cancer include radiation, surgery, chemotherapy, hormonal therapy, immunotherapy, biologic therapy and cryosurgery [2]. The treatments with cancer chemotherapeutic drugs are often associated with a variety of serious and non-serious ADRs. The most common side effect of chemotherapy administration is nausea with or without vomiting, diarrhea, alopecia, darkening of skin and nails, darkening of the injection site, myelosuppression, mucositis, gonadal dysfunction, hyper-uricemia, neuropathy, cardiomyopathy, hemorrhagic cystitis, impaired renal function, electrolyte imbalance, etc [3].

The objectives of ADR monitoring include detection of unknown drug-related safety problems, identification, and quantification of risk factors associated with the use of drugs and prevention of patients from being affected unnecessarily. The information pertaining to ADRs can be used to formulate therapeutic guidelines, public health policy decision and in pharmacoeconomic research. Based on these facts the regulatory authorities can bring about changes in package inserts and restrict the use of drugs or withdraw drugs from the market [2]. The analysis of ADRs associated with the cancer chemotherapy in a hospital set up gives an insight regarding the causality, severity, and preventability of the identified ADRs. It may also create awareness among the treating physicians. This can prevent future occurrence of similar ADRs in the same patient. Hence, this study was undertaken to analyze the ADRs identified in an oncology unit of a tertiary care teaching hospital.

A prospective observational study was carried out in the oncology department of Justice K S Hegde Charitable Hospital at Mangalore over a period of eight months. A total of 120 patients were enrolled in the study. All hospitalized patients of age 18 y and above and who were on cancer chemotherapy were included in the study. Patients using an alternative system of medicine such as ayurveda and homeopathy, subjects being treated as out-patient and mentally challenged subjects were excluded from the study. The study was approved by the central ethics committee of Nitte University Ref No: NU/CEC/P. G.-03/2015. During the study period, the in-patients of the oncology ward diagnosed with all types of cancer and treated with all types of chemotherapeutic drugs were observed on a daily basis. When an ADR was suspected information regarding patients demographics, diagnosis, drug therapy, relevant investigational reports were collected and documented in a suitably designed patient data collection form and ADR reporting form after obtaining the informed consent. It was then discussed with the treating physician for detailed evaluation. Once the ADR is confirmed it was analyzed for causality using WHO probability scale and Narajo's algorithm. The severity was analyzed by using Hartwigs severity scale, and preventability was assessed by using Modified Shomock and Thoronton scale. The management of the identified ADR was studied. The outcome of the ADR was then documented. Data analysis was carried out using statistical package for social sciences (SPSS) 16.0. Descriptive statistics was applied for analysing the collected data.

Among 120 cancer patients followed 58 (48.3%) male and 62 (51.7%) female received chemotherapy for a duration of eight months. A Hundred patients developed a total of 161 ADRs out of which 54(54%) were female, and 46 (46%) were male. This shows that incidence of ADRs was more common in female patients. The prevalence of cancer in the age group of 50-59 was found to be higher 42(35%). Highest distribution pattern of cancer among the

patients were found to be carcinoma of breast 28(23.3%) followed by buccal mucosa 13(10.83%), ovary 12(10.0%), tongue 8(6.6%), stomach 8(6.6%), cervix 7(5.83%), oropharynx 7(5.83%), glottis 7(5.83%), colon-rectal 7(5.83%), esophagus 6(5.0%), lung 5(4.16%), lymphoma 4(3.33%), pancreas 3(2.5%), alveolus 3(2.5%) and testis 2(1.6%). Out of 120 patients who received chemotherapy 43(35.08%) patients were administered with Cisplatin followed by FAC 25 (20.8%), PC 19(15.8%), 5-FU 11(9.2%), CHOP 6(4.2%). details of chemotherapy regimen is provide in table 1.

Table 1: Pattern of chemotherapy regimen prescribed

Chemotherapy regimen	Frequency	Percentage
Cispltin	43	35.8
5Fluro uracil+Adriyamycin+Cyclophosphamide (FAC)	25	20.8
Paclitaxel+Carboplatin	19	15.8
5-Flurouracil (5-Fu)+Leucoverin	11	9.2
Cyclophosphamide+Doxorubicin+Vincristine+Prednisone(CHOP)	6	4.2
Oxaliplatin+Capecetabine	5	4.1
Carboplatin	3	2.5
Paclitaxel	3	2.5
Adriyamycin+cyclophosphamide (AC)	1	0.8
Doxorubicin	1	0.8
Cisplatin+Etoposide	1	0.8
Epirubicin+Oxaliplatin	1	0.8
Cyclophosphamide+Adriyamycin+Vincristine	1	0.8
5-Flurouracil+Cyclophosphamide+Methotrexate	1	0.8
Total	120	100

A total of 161(83.33%) ADRs were observed in patients receiving chemotherapy. Adverse effect on the hematological system was more commonly seen in patients 61(37.88%) followed by gastrointestinal effects 44 (27.32%), central nervous system and peripheral nervous system 16(9.93%). Refer table 2.

Table 2: Identified ADRs and organ system affected

Organ system involved	Adverse drug reaction	Frequency	Percentage
Blood	Anemia	34	21.1
	Leucopenia	20	12.4
	Neutropenia	2	1.2
	Thrombocytopenia	3	3.1
	Thrombocytosis	2	1.2
Cardiovascular system	Hypotension	4	2.5
CNS and PNS	Fever and chills	7	4.3
	Headache	6	3.7
	Tingling and numbness	3	1.9
Gastrointestinal system	Anorexia	4	2.5
	Constipation	6	3.7
	Diarrhea	4	2.5
	Fatigue	2	1.2
	Heartburn	3	1.9
	Mouth sore	4	2.5
	Mucositis	11	6.8
	Nausea	4	2.5
	Vomiting	6	3.7
Musculoskeletal system	Limb edema	1	0.6
	Muscle and joint pain	6	3.7
Renal system	Hyperuricemia	4	2.5
	Hypokalemia	3	1.9
	Hypocalcaemia	2	1.2
	Hypomagnesaemia	1	0.6
	Hypervolemia	1	0.6
Respiratory system	Cough	6	3.7
Skin and appendages	Itching	2	1.2
	Nail discoloration	4	3.1
	Skin color changes	5	3.1
Sensory system	Tinnitus	1	0.6
Total no of ADRs		161	100

Cisplatin 63(39.1%) was the most commonly prescribed individual class of drug and found to be the cause of most of the ADRs occurred when compared to other class of individual and combination drugs. Refer fig. 1.

The causality assessment of reported ADRs was done using WHO UMC Scale and Naranjo's algorithm. WHO UMC Scale revealed that majority of the ADRs were probable 87 (54.0%) followed by possible 48(29.8%), certain 21(13.0), and unlikely 5(3.1%). Naranjo's algorithm showed that majority of the ADRs were probable 98(60.9%), followed by possible 50(31.1%), definite 9(5.6%), and doubtful 4(2.5%).

The severity level was assessed using Hart wig severity scale according to which 96(59.2%) ADR were moderate, 67(41.61%) were mild and 2(1.2%) were found to be severe, no fatal reactions were reported in the study. As per the Modified Shumock and Thornton preventability scale 122(75.8%) reactions were not preventable, 31(19.3%) were probably preventable and 8(5.0%) were definitely preventable.

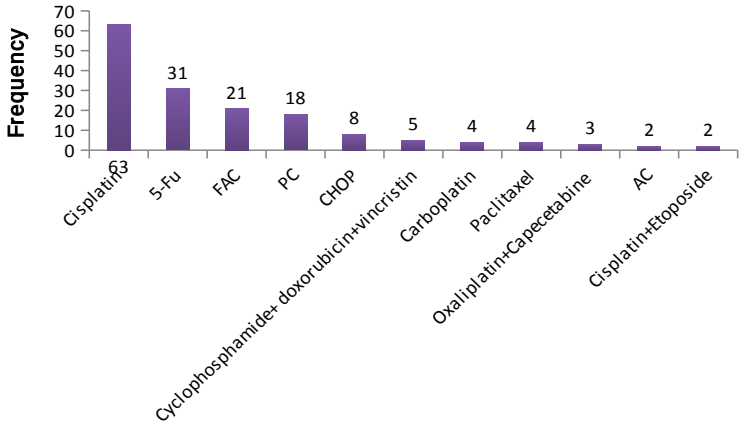

Fig. 1: ADRs caused by chemotherapy regimen

The ADRs were managed by different approaches to reduce the severity level, 63.35% of the ADRs were managed by providing additional treatments without making any changes in the drug regimen, 38.04% ADRs were managed with no additional treatment and in the case of 13.04% ADRs the chemotherapy was post ponded due to the severity of the ADR. Specific treatment was given to 40.4% patients, symptomatic treatment to 36% of patients and 23.6% of patients did not receive any drug therapy for the ADRs. Refer table 3.

Different classes of drugs were used for the management of each ADR. Filagristin, blood transfusion and iron preparations which were given to increase the blood count. Septilin was given as an immunomodulator, loperamide for diarrhoea, normal saline and parenteral preparation of potassium and calcium chloride for the management of electrolyte imbalance.

Acetaminophen, mefenamic acid, and diclofenac sodium were prescribed for pain management. Vitamin B complex and multivitamin tablets were used for the symptomatic relief of anorexia, tingling, and numbness. Aluminum hydroxide, magnesium hydroxide, itopride, and sucralfate were used to treat gastric ulcers.

Table: 3 Management of the identified ADRs

Management	Frequency	Percentage (%)
Pattern of drug therapy for the identified ADRs		
Specific	65	40.4
Symptomatic	58	36.0
Nil	38	23.6
Management of ADR		
No change in drug regimen but additional treatment was given	122	75.77
Drug withdrawn/Chemo post ponded	21	13.04
No change in drug regimen and no additional treatment	18	11.18
Outcome of ADR Management		
Recovery	133	81.40
Continuing	24	14.90
Unknown	6	3.7

The current study analyzed the adverse drug reactions due to cancer chemotherapeutic agents. The incidence of ADRs in our hospital during the study period was 83.33%. This is comparable to study conducted in a tertiary care teaching hospital in eastern India by Prasad *et al.* [7] where they reported an incidence of 86.53%. In the current study hematological system was most commonly affected 61(37.88%) because of the non-selective action of chemotherapeutic drugs. They target the rapidly dividing cells of bone marrow along with the tumor cells which eventually causes bone marrow suppression leading to anemia, leucopenia, neutropenia and thrombocytopenia.

This finding is consistent with the study conducted by Khandelwal *et al.* [5] But it is in contrast with the study conducted by Poddar *et al.* [7] wherein gastrointestinal system was most commonly affected. Adverse drug reactions such as nausea and vomiting were less reported in the present study since it was well managed with adequate pre-medication. Parenteral dexamethasone, ranitidine, and ondansetron before chemotherapy and daily 3 doses of ondansetron were given orally for three consecutive days to the patient for preventing early and late stage emesis after the chemotherapy. It is clear from this that it is easy to predict a known ADR and therefore measures can be taken to prevent the same.

Cisplatin, carboplatin, paclitaxel, doxorubicin, and cyclophosphamide were more commonly associated with adverse drug reactions because its act primarily in rapidly dividing tissues such as bone marrow, gastrointestinal tract, mucosal cells and reproductive system. This finding is similar to the study carried out by Goyal *et al.* [3] and Prasad *et al.* [7] According to WHO causality assessment scales most of the reported ADRs were probable (54.0%). This finding is in contrast to the study conducted by Goyal *et al.* [3] in which ADRs belonged to the category possible (39.0%). Causality assessment of adverse effect was also done utilizing the Naranjo's scale where 60.9% ADRs was found to be probable, 31.1% were possible, and 5.6% were definite. This finding was similar to the study carried out by Prasad *et al.* [7].

As per Hartwig SC et. al severity scale 59.62% ADRs were moderate followed by mild (41.61%) and severe (1.2%). This finding is in consonance with the study conducted by Khandelwal *et al.* [5] wherein 47.77% were moderate followed by mild and severe reactions. The findings of 5.0% ADRs being definitely preventable followed by 19.3% of probably preventable was comparable with the results of a study by Khandelwal *et al.* [5] where 81.1% were not preventable followed by 18.0% of probably preventable reactions. The management strategy resulted in an outcome of complete

recovery in 81.40% of patients whereas 14.91% of patients did not recover from the ADRs. The outcomes of 6 ADRs were unknown due to the unavailability of complete data of the patients because of their immediate discharge after chemotherapy.

This study provides baselines characteristics of ADRs due to cancer chemotherapy. The incidence of adverse drug reaction associated with the chemotherapeutic agent was found to be higher as it has a narrow therapeutic index. These ADRs can be minimized by early detection, reducing drug toxicity, modifying the doses or drug regimens that implicate adverse effect. The study report states that when patients have chemotherapy with individual drugs, especially, Cisplatin, 5-Fluro uracil and combination drug regimens which include FAC, CHOP, and PC they should be strictly and continuously monitored for the symptoms of ADRs. The results of this study highlight the importance of monitoring the in patients on cancer chemotherapy for any signs of ADRs. The early detection and prompt management of these ADRs can reduce its health-related and economic effects on the patients. We observed that these patients and their family members required good counseling regarding the adverse effects of the cancer chemotherapy. In many cases alopecia, skin and nail discolouration, loss of appetite caused a lot of frustration and emotional instability among the patients and their bystanders. The study had some limitations like the small sample size and short duration. The ADRs were monitored manually the electronic reporting of ADRs could have generated more reports from the ward physicians and nurses.

CONFLICT OF INTERESTS

Declared none

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