Original Article

Pattern of adverse drug reactions due to cancer chemotherapy in a tertiary care hospital in South India

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Abstract

Purpose: Studies regarding pattern of adverse drug reactions (ADRs) in cancer chemotherapy patients are scarce in India. This study was conducted to evaluate the pattern of occurrence of ADRs due to cancer chemotherapy in hospitalized patients and to assess the causality, severity, predictability, and preventability of these reactions. **Materials and Methods:** This was a retrospective, descriptive study and the occurrence and nature of ADR, suspected drug, duration of hospital stay and outcome were noted from case records. These ADRs were assessed for causality using both World Health Organization (WHO) causality assessment scale and Naranjo's algorithm. The severity and preventability of the reported reactions were assessed using modified Hartwig and Siegel scale and modified Schumock and Thornton scale respectively. **Results:** Five hundred ADRs were recorded from 195 patients. Most common ADRs were infections (22.4%), nausea/vomiting (21.6%) and febrile neutropenia (13%). Platinum compounds, nitrogen mustards, taxanes, antibiotics and 5-fluorouracil were the most common drugs causing ADRs. WHO causality assessment scale showed 65% of the reactions to be "probable" and 35% to be "possible," while Naranjo's algorithm indicated that 65.6% of ADRs were "probable" and 34.4% were "possible". Modified Hartwig and Siegel scale showed most reactions (41.4%) to be of "moderate level 4(a)" severity, while 30.6% of reactions were of "mild level 1" severity. About 30.8% of the ADRs were "definitely preventable" according to the modified Schumock and Thornton scale. **Conclusion:** ADRs are most important causes of morbidity and mortality and increase the economic burden on patient and society. By careful ADR monitoring, their incidence can be decreased.

Key words: Adverse drug reactions, causality, chemotherapy, pharmacovigilance

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INTRODUCTION

An adverse drug reaction (ADR) is any undesirable or unintended consequence of drug administration. A major portion of the increasing health care costs and human suffering can be attributed to ADRs.[1] The World Health Organization (WHO) defines an ADR as "any response to a drug, which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy".[2] The field of cancer chemotherapy has

undergone a drastic change in the past four decades with curative treatment being discovered for formerly fatal malignancies, such as lymphomas, leukemias and testicular cancers. Chemotherapy is employed as part of a multimodal approach to the treatment of many tumors and it has been revolutionized with the advent of newer drugs.[3]

The science dealing with detecting, assessing and preventing ADRs has been termed "pharmacovigilance".[4] Providing efficient health care to the public is met with various challenges and the frequent occurrence of drug toxicity is a major setback in this context. ADRs can prolong the patient's recovery as well as cause hospitalization and thereby increase the suffering. With the marketing of thousands of drugs every year and over-enthusiastic prescription, it is crucial that we identify ADRs as early as possible and prevent them if possible, to ensure the well-being of the patient at a reasonable cost. The WHO realized the importance of having an efficient, dynamic surveillance system to monitor the occurrence of ADRs, which was the basis for starting the International Drug Monitoring Program. The Pharmacovigilance Program of India was started in India in 2010 with the objectives of monitoring drug safety and creating an ADR database for our population.[5]

Hospital-based ADR monitoring and reporting programs can help in identifying and assessing the risks associated with the use of drugs. This data may help the prescribers to identify ADRs and deal with them more efficiently, and also help in preventing the occurrences of these ADRs in future.[6] ADR monitoring and reporting activity is still in the early stages in India. Lack of an organized and efficient ADR monitoring and reporting program is posing a great challenge to drug safety screening in the Indian subcontinent.[7] Lack of awareness and fear of litigations on the part of the prescriber are main causes for under-reporting of ADRs. Scarcity of studies relating to drug safety monitoring in India led us to undertake this study where we tried to evaluate the pattern of ADRs occurring in cancer patients treated with chemotherapy in a tertiary care hospital in South India.

MATERIALS AND METHODS

This retrospective, descriptive, case record study was conducted on patients admitted to the Medical Oncology ward of the tertiary care hospital, after obtaining the approval of the Institutional Ethics Committee. Of 462 patients who received chemotherapy during the study period of 2 years, from January 1, 2011 to December 31, 2012, 195 serial cases developing ADRs were included in this study as the study aimed at analyzing 500 ADRs. Though the institution is an ADR monitoring center, the data were collected from the medical records section of the study center. The data regarding ADRs was directly collected from patients and reports of laboratory investigations and duly recorded in the case records by the doctors and residents of Medical Oncology Department. Patients of both sexes and all ages diagnosed with cancer and treated with chemotherapy for the same, developing at least one ADR during or after the treatment period were included in the study. Patients who developed ADR due to fresh blood or blood products infusion, or due to intentional or accidental poisoning and those with a history of drug abuse and intoxication were excluded from the study.

The demographic details of the patients were recorded. Details of the medications given were duly noted. Details regarding the occurrence and nature of ADR, suspected drug, duration of hospital stay and outcome were carefully recorded. Relevant laboratory investigation values were also noted. The reported ADRs were assessed for causality using both WHO causality assessment scale[8] and Naranjo's algorithm.[9] The severity of the reported reactions was assessed using modified Hartwig and Siegel scale.[10] The predictability and preventability of the reported ADRs were assessed using developed criteria for determining predictability of an ADR and Modified Schumock and Thornton scale respectively.[11]

The WHO causality assessment scale determines the causal relationship of a suspected drug to the ADR in question and causality is categorized into "certain," "probable," "possible," "unlikely," "conditional/unclassified" and "unassessable/unclassifiable." Naranjo's algorithm has 10 objective questions with three options for answers - yes, no, do not know. Scores are given accordingly and the causality of the drug can be classified as "definite," "probable," "possible," and "unlikely." The modified Hartwig and Siegel scale classifies severity of ADR as "mild," "moderate," or "severe" with various levels, depending on a number of factors like the requirement for change in treatment, duration of hospital stay and the disability produced by the ADR. The developed criteria for determining predictability of an ADR categorizes ADR as "predictable" or "not predictable" based on the incidence rate of reported ADR and history of allergy or previous reaction to the drug. The modified Schumock and Thornton scale determines the preventability of an ADR and classifies them as "definitely preventable", "probably preventable" and "not preventable". The data collected were analyzed with the help of SPSS software version 17.0 developed by IBM and frequencies were determined for each variable.

RESULTS

Among the 195 patients included in the study, 109 (55.9%) were females and 86 (44.1%) were males. Majority of the cases were seen in the age group of 51-60 years (26.2%). 141 (72.3%) patients were married. Most of them were housewives (44.1%) or students (24.6%), while the others were manual laborers (12.8%), skilled workers (7.7%), agriculturists (5.7%), businessmen (3.6%) or lecturers (1.5%) by profession. Most of them (82.6%) had never smoked, while some (13.8%) were ex-smokers and a few others (3.6%) were current smokers [Table 1]. The most common cancers diagnosed were non-Hodgkin's lymphoma (19.6%), followed by ovarian cancer (14.6%), breast cancer (12.8%), sarcoma (10.6%), and Hodgkin's lymphoma (7.8%) [Figure 1].

A total of 500 ADRs were identified and recorded in the study subjects. Most commonly occurring ADRs were infections (22.4%), nausea/vomiting (21.6%), febrile neutropenia (13%) and anemia (7.2%) [Figure 2]. Majority (51%) of the study population was treated with platinum compounds. Most of the patients (46.8%) were treated with chemotherapy only, while some (33.2%) were treated with surgery in addition to chemotherapy, a

Table 1: Demographic details of patients (*n*=195)

Variable	Number	Percentage
Gender		
Male	86	44.1
Female	109	55.9
Age in years		
0-10	27	13.8
11-20	19	9.7
21-30	14	7.2
31-40	24	12.3
41-50	30	15.4
51-60	51	26.2
61-70	23	11.8
71-80	7	3.6
Marital status		
Married	141	72.3
Unmarried	54	27.7
Smoking		
Never	161	82.6
Ex-smoker	27	13.8
Current smoker	7	3.6

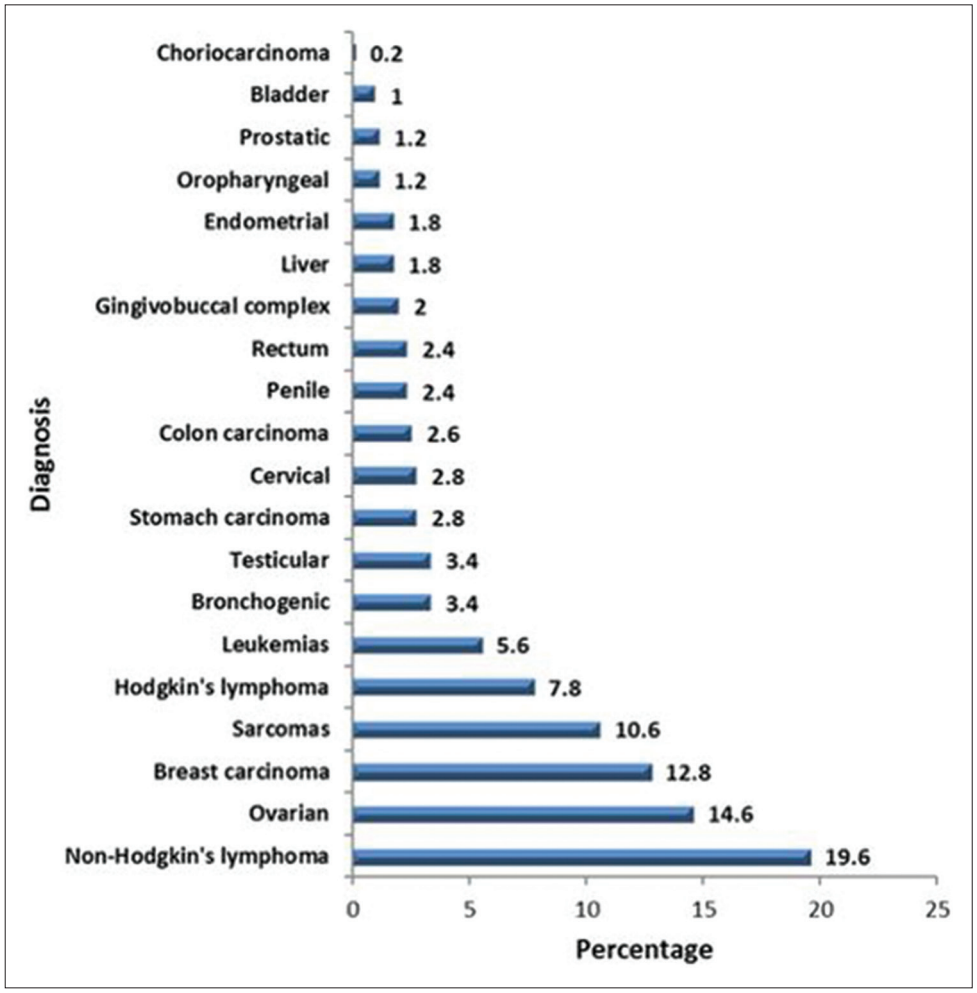

Figure 1: Distribution of cancers in the study population (*n* = 195)

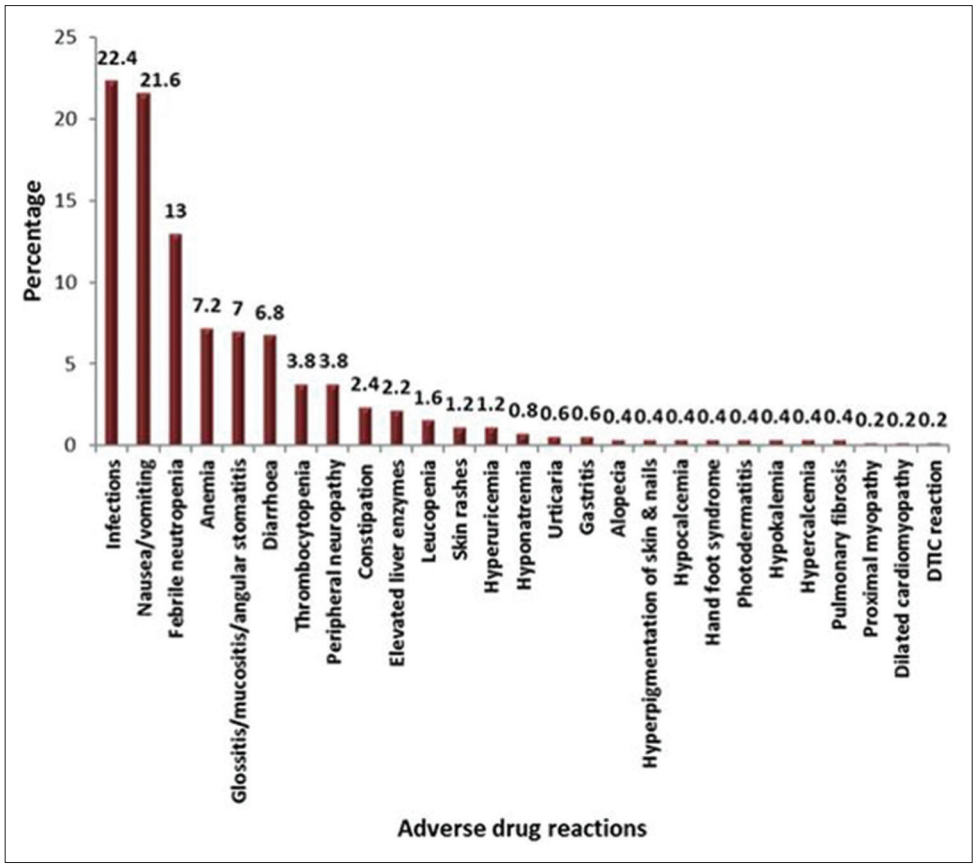

Figure 2: Pattern of adverse drug reaction developed (*n* = 500)*. **n* = Total number of adverse drug reactions

few (6.4%) were treated with radiotherapy in addition to chemotherapy and the others (13.6%) were treated with a combination of surgery, radiotherapy, and chemotherapy. Platinum compounds (24.2%), nitrogen mustards (20.6%), taxanes (17%), antibiotics (6.6%) and 5-fluorouracil (5%) were the most common drugs causing ADRs [Figure 3].

Assessment of causality by WHO causality assessment scale indicated that 65% of the reactions were "probable" and 35% were "possible". There were no "certain" ADRs as re-challenge was not attempted in any of the patients. According to Naranjo's algorithm, 65.6% of the reactions were "probable" with a score ranging from 5 to 8 and 34.4% were "possible" with a score ranging from 1 to 4. The causality assessment of individual ADRs by both WHO causality assessment scale and Naranjo's algorithm, is shown in Table 2. The severity of the reported reactions was assessed using modified Hartwig and Siegel scale and accordingly, most of the ADRs (41.4%) were categorized as "moderate level 4(a)" severity, followed by "mild level 1" (30.6%), "moderate level 4(b)" (22%), "severe level 6" (4%) and "severe level 5" and "severe level 7" (1% each). The developed criteria for determining predictability of an ADR determined most of the ADRs (95.8%) to be "predictable" and the rest were "not predictable" (4.2%). The modified Schumock and Thornton scale determined most of the ADRs (65.4%) to be "not preventable," while some (30.8%) of the reactions like nausea/vomiting and constipation were "definitely preventable" and others like diarrhea, glossitis, mucositis and febrile neutropenia were "probably preventable" (3.8%).

DISCUSSION

Over the past few decades, the development of newer antineoplastic agents has added to the ammunition of oncological treatment, but has also increased the occurrence of ADRs. New ADRs are often discovered when drugs are used in larger or in different populations than studied during initial clinical trials. This typically occurs within 3 years of the drug entering the market. Therefore, documentation and reporting of ADRs becomes a crucial element in clarifying the side-effect profile of a drug. This may help to prevent future occurrences of such incidents. A noble, ethical medical practice needs accurate and unbiased information about drugs. This is possible only by a vigorous drug safety monitoring program.[2] An efficiently operating hospital-based reporting program may be helpful in providing an insight into the potential problems of drug usage in an institution. Through these

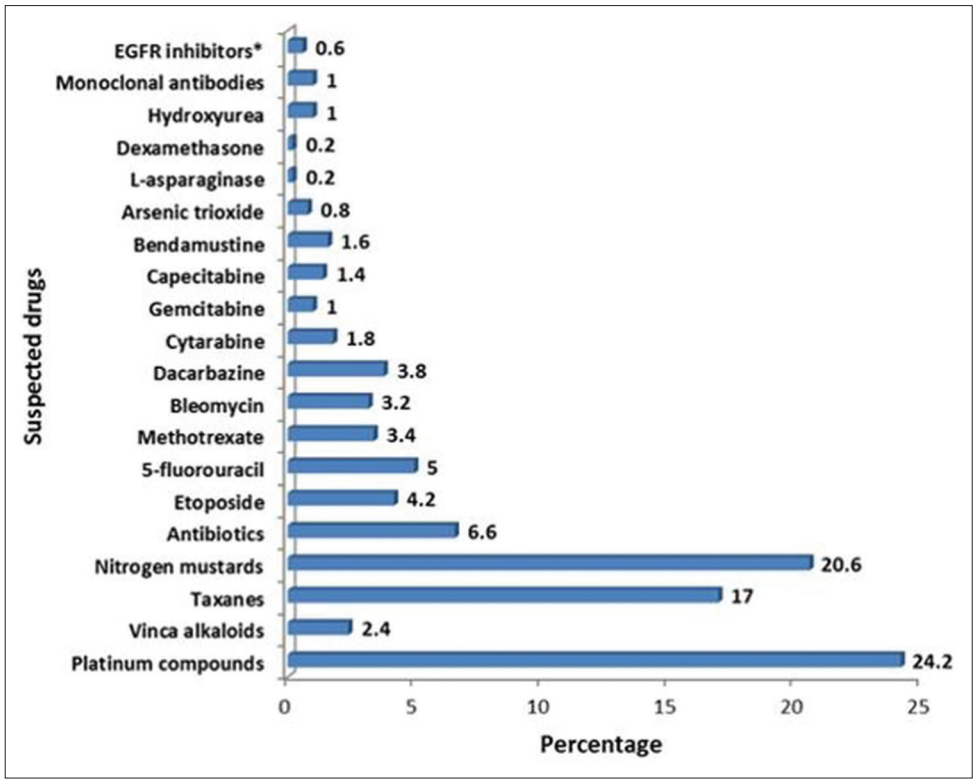

Figure 3: Suspected drugs causing the adverse drug reactions (*EGFR inhibitors-Epidermal growth factor receptor inhibitors)

efforts, problems can be identified and resolved, resulting in continuous improvement in patient care.[12]

In our study, we evaluated the pattern of ADRs occurring in cancer chemotherapy patients. We found that the majority of the patients were females (55.9%) which is consistent with findings in other studies.[1,5] However in some other studies a male preponderance was seen.[13,14] The increased incidence of ADRs in females may be attributed to the alteration occurring in the pharmacokinetics of the drugs due to hormonal changes during different stages of life, like puberty and pregnancy.[15,16] Most of the ADRs were seen in patients in the age group of 51-60 years (26.2%) which is again similar to reports of studies done by Poddar *et al.* and Prasad *et al.*[1,13] This could be due to the fact that in elderly patients, the metabolizing capacity and the excretory functions are reduced, leading to accumulation of drugs in the body and thus increasing the risk of ADRs.[17]

Majority of the patients (82.6%) were nonsmokers. Similar results were reported by Poddar *et al.*[1] Most common cancers diagnosed were non-Hodgkin's lymphoma (19.6%), followed by ovarian cancer (14.6%) and breast cancer (12.8%) in our study. However in other studies breast cancer and bronchogenic carcinoma were found to be commonest.[1,13] In India, most common cancer among males is oro-pharyngeal cancer followed by bronchogenic carcinoma. Among females most common cancer in India is cervical cancer followed by breast cancer. These differences found in our study may be due to variations in food habits and lifestyles in different geographical locations.

Commonest ADRs found were infections (22.4%), nausea/vomiting (21.6%) and febrile neutropenia (13%). Few other studies reported nausea and vomiting as the most common ADR.[1,13] Studies carried out by Mallik *et al.* reported neutropenia as the most common ADR, while study conducted by Lau *et al.* reported constipation to be commonest ADR.[14,18] Cancer chemotherapy damages rapidly dividing cells of bone marrow resulting in myelosuppression thus affecting white blood cells, platelets and red blood cells. This myelosuppression leads to a lowering of immunity and thus patients on cancer chemotherapy are at a high risk for developing various infections. Nausea and vomiting are prominent with most cytotoxic agents and is caused mainly due to direct stimulation of chemoreceptor trigger zone.

Most of the patients (46.8%) were treated with chemotherapy only, while some needed additional therapy such as surgery (33.2%), radiotherapy (6.4%) or a combination of surgery and radiotherapy (13.6%). The different treatment plans adopted depend upon a variety of factors such as the staging of the cancer, cost of the treatment plan, patient and physician related factors. ADRs occurring

Table 2: Causality assessment of individual adverse drug reaction

Adverse drug reaction	Number of adverse drug reactions					
	WHO causality assessment scale			Naranjo's algorithm		
	Possible	Probable	Total	Possible	Probable	Total
Nausea/vomiting	108	0	108	108	0	108
Constipation	12	0	12	12	0	12
Diarrhoea	34	0	34	33	1	34
Glossitis/mucositis/angular stomatitis	0	35	35	0	35	35
Gastritis	0	3	3	0	3	3
Alopecia	0	2	2	2	0	2
Hyperpigmentation of skin and nails	0	2	2	0	2	2
Anemia	4	32	36	0	36	36
Febrile neutropenia	0	65	65	0	65	65
Leucopenia	0	8	8	0	8	8
Thrombocytopenia	0	19	19	0	19	19
Peripheral neuropathy	0	19	19	0	19	19
Skin rashes	0	6	6	0	6	6
Proximal myopathy	0	1	1	0	1	1
Infections	1	111	112	1	111	112
Urticaria	0	3	3	0	3	3
Hand foot syndrome	0	2	2	0	2	2
Photodermatitis	0	2	2	0	2	2
Dilated cardiomyopathy	0	1	1	0	1	1
Hypokalemia	2	0	2	2	0	2
Hyperuricemia	6	0	6	6	0	6
Elevated liver enzymes	0	11	11	0	11	11
Hypercalcemia	2	0	2	2	0	2
Hypocalcemia	2	0	2	2	0	2
Hyponatremia	4	0	4	4	0	4
Pulmonary fibrosis	0	2	2	0	2	2
DTIC reaction	0	1	1	0	1	1
Total	175	325	500	172	328	500

WHO=World Health Organization, DTIC=Dacarbazine

only due to chemotherapy were taken into consideration in this study. The most comon drugs causing ADRs were platinum compounds (24.2%), nitrogen mustards (20.6%), taxanes (17%), antibiotics (6.6%) and 5-fluorouracil (5%). This is in accordance with reports from other similar studies.[1,13,14]

In this study, most of the reactions showed a similar causality assessment by both WHO causality assessment scale and Naranjo's algorithm except for diarrhea and anemia, which were assessed as "possible" with lower level of causality by WHO scale, were judged as "probable" with higher level of causality by Naranjo's algorithm. There were no "certain" reactions as re-challenge was not attempted in any of the patients. The grade of causality remained low due to a number of co-administered drugs. There were no "unlikely" reactions as the investigator was trained in the methods of pharmacovigilance and such complaints were avoided.

Most of the reactions were of mild to moderate severity and did not warrant stoppage or changing of drug. Similar studies may be used to identify iatrogenic adverse effects and may help in preventing such occurrences in the future. Most of the ADRs (95.8%) were "predictable," which is in concordance with reports from study done by Lau *et al*.[18]

While most of the ADRs were "not preventable," some of the reactions like nausea/vomiting and constipation were "definitely preventable" and the others such as diarrhea, glossitis, mucositis and febrile neutropenia were "probably preventable." These findings again corroborate the findings reported by Lau *et al*.[18]

This study provides basic information regarding the safety profile of various anticancer drugs in a variety of cancers. We have also assessed four different parameters of the ADR noted, namely the causality, severity, predictability, and preventability. Other studies have focused on either a single drug or only on the causality aspect.[5,13,14] To the best of our knowledge, this is the first study of its kind from South India. While most of the ADRs were "predictable," the others like cases of electron imbalance, mainly hypokalemia and hypocalcemia were "not predictable"; though there are some reports of it, which cannot be considered conclusive. This again highlights the importance of a continued rigorous screening of drug safety profile.

A major limitation of the study is that we analyzed only 500 ADRs and this did not cover all the patients receiving chemotherapy during the study period. Since it was a retrospective study, there are chances of under-reporting

and incomplete documentation of data regarding ADRs in the case records.

CONCLUSION

Cancer chemotherapeutic agents have a high propensity to cause ADRs as they are toxic to rapidly dividing cells in the body. Nevertheless, an early detection of these ADRs may help in minimizing the damage by either modifying the dose or changing the offending agent. This knowledge can also prevent the occurrence of similar such reactions in the future. There is a great need to set up an effective ADR monitoring and reporting system in all hospitals and also create awareness among health care professionals 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 assuage human suffering and reduce economic burden to the patient and society.

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