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Original Article

Chemotherapy Induced Adverse Drug Reactions in Cancer Patients in a Tertiary Care Hospital in South India

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ABSTRACT

Objective: To evaluate the pattern of adverse drug reactions (ADRs) reported in cancer patients receiving anticancer drugs in an adverse drug reaction monitoring centre (AMC). **Methods:** The anticancer drug related ADRs received in AMC through spontaneous reporting and active surveillance methods from January 2014 to June 2016 were analyzed for demographic profile, organ system and department wise distribution of ADRs, common ADRs encountered, drugs responsible for causing ADRs, ADRs reported by healthcare professionals, number of ADR/ ADRs developed per patient and causality assessment of reported ADRs. Descriptive statistics were used for analysis and the values were expressed in numbers and percentages. **Results:** 2209 ADRs were reported from 1869 patients comprising of 764 males (40.88%) and 1105 females (59.12%). In our study, the most common ADRs observed were anemia (12.68%), neuropathy (11.18%) and neutropenia (6.07%). Causality assessment of ADRs by WHO-UMC causality scale revealed that 90.9% of ADRs were possible followed by 4.48% probable and 2.39% possible. The most common organ system wise classified ADRs were blood (24.22%) related reactions followed by gastrointestinal system (14.17%) related adverse effects. The most common drugs associated with ADRs were imatinib (13.94%) followed by docetaxel (9.55%), gemcitabine (8.56%) and paclitaxel (7.38%). Amidst 1869 patients, 301(13.63%) patients had developed two ADRs while 39 (1.76%) patients experienced three ADRs. **Conclusion:** The average ADR encountered per patient due to anticancer drug was about 1.18 in this study. Anemia, neuropathy and neutropenia were the most common ADRs reported.

Key words: Anticancer drugs, Chemotherapy, Tertiary care hospital, ADR monitoring centre (AMC).

Key message: Cancer is one of the leading causes of death globally. Owing to narrow therapeutic window, patients taking anticancer drugs have higher risk for developing adverse drug reactions. Hence a study is needed to evaluate the occurrence of adverse drug reactions caused by anticancer drugs.

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INTRODUCTION

Cancer is one of the leading causes of death in both developed and developing countries.[1] According to International Agency for Research on Cancer, GLOBOCAN 2012, an estimated 14.1 million new cancer cases and 8.2 million cancer-related deaths occurred in 2012 and new cancer cases may increase to 19.3 million per year by 2025.[2] Chemotherapy, radiotherapy, surgery, hormonal therapy, immunotherapy, biologic therapy and cryosurgery are the different treatment modalities available for cancer. Chemotherapy, immunotherapy and hormonal therapy are the treatment options in the early stages of cancer.[3] As anticancer drugs have narrow therapeutic index, adverse drug reactions (ADRs) to these medications are high compared to other classes of drugs. According to WHO, adverse drug reaction (ADR) is defined as "any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."[4] According to an epidemiological research performed in Australia, antineoplastic and immunosuppressive drugs are associated with 11% of adverse drug reactions (ADRs) in Australian hospitals with antineoplastic drugs being the most common agents responsible for medication-related hospitalizations.[5] Similarly a study conducted in South Indian hospital has reported antineoplastic agents as the common class of drugs causing ADRs accounting for a total of 21.8% of the reported ADRs.[6] A recent study on global patterns of ADRs over a decade has documented that high-income countries have more ADRs from antineoplastic and immune-modulating agents.[7]

In addition to increasing the length of hospital stay, ADRs also significantly increase the health cost. The estimated total cost of treatment for ADRs is 1.7% of the total hospital budget with a median cost of 8517 francs.[8] Most of the ADRs with these drugs are unreported due to unawareness of healthcare professionals, lack of time to report and a dearth of sufficient staff in the hospitals. Hence it is necessary to recognize the pattern of ADRs occurring with anticancer drugs so as to enhance the quality of life and to reduce the cost of ADR related hospitalization among cancer patients. Thus the present study is aimed to determine the pattern of adverse drug reactions occurring with anticancer drug in a tertiary care hospital.

MATERIALS AND METHODS

Adverse drug reactions reported to the ADR monitoring Centre (AMC) functioning in a tertiary care South Indian hospital from January 2014 to June 2016 were collected. Among the ADRs reported to AMC during this period, ADRs related to anticancer drugs were segregated and analyzed. ADR due to anticancer drugs reported to AMC by both spontaneous

reporting and active surveillance methods were included. Though spontaneous reporting by healthcare professionals is the common method of reporting, active surveillance plays a significant role in detecting newer and rare ADRs within a short period.[9] Hence, ADRs reported by both the methods were included for analysis. Suspected adverse drug reaction reporting form was used by AMC for reporting of ADRs as a part of the Pharmacovigilance program of India (PvPI). The ADRs were classified as certain, probable, possible, unlikely, unclassified or unclassifiable using WHO-UMC causality assessment scale.[4] Causality assessment was done by a team of Clinical Pharmacologists and Pharmacovigilance Associate (PA) working under Pharmacovigilance Programmer of India (PvPI). As and when required the opinion of the consultants of concerned departments were taken into consideration for the causality assessment. All the data were presented in percentage.

RESULTS

A total of 2209 ADRs with cancer chemotherapy were reported from 1869 cancer patients during the study period. Among the ADRs reported 882 (39.93%) were in males and 1327 (60.07%) were in females as shown in Figure 1. Further analysis based on age, revealed more ADRs in the age group of 41-60 years (942, 59.4%) compared to (163, 8.7%) in the age group of 0-18 years as shown in Figure 2.

Department wise distribution of ADRs

Most of the ADRs were collected from Regional cancer centre (RCC), JIPMER (2122, 96.06%) followed by Medicine (29, 1.31%), Clinical immunology (21, 0.96%), Nephrology (12, 0.54%), Pharmacology (11, 0.49%) and Dermatology (2, 0.09%) as shown in Table 1.

Organ system wise distribution of ADRs

The present study showed that in both males and females, the most affected organ system was blood (553, 24.22%) followed by skin and appendages (366, 16.57%), gastrointestinal (313, 14.17%) and neurological disorder (301, 13.63%). The least common ADRs noticed were congenital, hearing, vestibular and senses, white and red cell disorders shown in Table 2.

Types of adverse drug reactions (ADRs)

Most common ADRs encountered were anemia (280, 12.68%) followed by neuropathy (247, 11.18%), neutropenia (134, 6.07%), thrombocytopenia (126, 5.7%), myalgia (121, 5.47), hand foot syndrome (HFS) (119, 5.39%) as shown Table 3.

Causality assessment of ADRs

According to WHO-UMC causality assessment scale, out of 2209 ADRs, 52 (2.36%) were certain, 2008 (90.9%) were possible, 99 (4.48%) were probable, 46 (2.08%) were unlikely and 4 (0.18%) were unclassified as shown in Figure 3.

Reporting of ADRs

Among the ADRs reported, 985 (44.59%) were actively collected by pharmacovigilance associate (PA) followed by spontaneous reporting from pharmacists (655, 29.65%), doctors (415, 18.79%), nurses (137, 6.20%) and PhD scholars (17, 0.77%) as shown in Figure 4.

Chemotherapeutic agents

The most common suspected chemotherapeutic agents causing ADRs in our setting was imatinib (308, 14.26%) followed by docetaxel (211, 9.71%), gemcitabine (189, 7.96%) and paclitaxel (163, 7.9%) as shown Table 4.

Table 1: Department wise distribution of ADRs

Sl. No.	Department	Number of ADRs	Percentage (%)
1	Regional Cancer Centre (RCC)	**2122**	96.06
2	Medicine	**29**	1.31
3	Clinical immunology	**21**	0.96
4	Nephrology	**12**	0.54
5	Pharmacology	**11**	0.49
6	Clinical pharmacology	**3**	0.13
7	Surgical oncology	**3**	0.13
8	Endocrinology	**2**	0.09
9	Dermatology	**2**	0.09
10	Cardiology	**1**	0.05
11	Radiology	**1**	0.05
12	Neurology	**1**	0.05
13	Orthopedic	**1**	0.05
Total		**2209**	100

Table 2: Organ system wise distribution of ADRs

No.	SYSTEM ORGAN CLASS	No. of ADRs	Percentage (%)
1	Blood disorders	535	**24.22**
2	Skin and appendages disorders	366	**16.57**
3	Gastrointestinal disorders	313	**14.17**
4	Neurological disorders	301	**13.63**
5	Musculoskeletal disorders	166	**7.51**
6	Body as a whole- general disorders	166	**7.51**
7	Vascular, bleeding and clotting disorders	98	**4.44**
8	Respiratory system disorders	79	**3.58**
9	CNS and PNS disorders	60	**2.72**
10	Psychiatric disorders	37	**1.67**
11	Liver and biliary disorders	17	**0.77**
12	Reproductive disorders	17	**0.77**
13	Cardiovascular disorders	16	**0.72**
14	Urinary system disorders	12	**0.54**
15	Metabolic and nutritional disorders	12	**0.54**
16	Immune disorders and infections	5	**0.22**
17	Vision disorders	3	**0.14**
18	Congenital disorders	1	**0.05**
19	Hearing, vestibular and senses disorders	1	**0.05**
20	White and red cell disorders	1	**0.05**
21	Information not found in the register	3	**0.13**
Total		**2207**	**100**

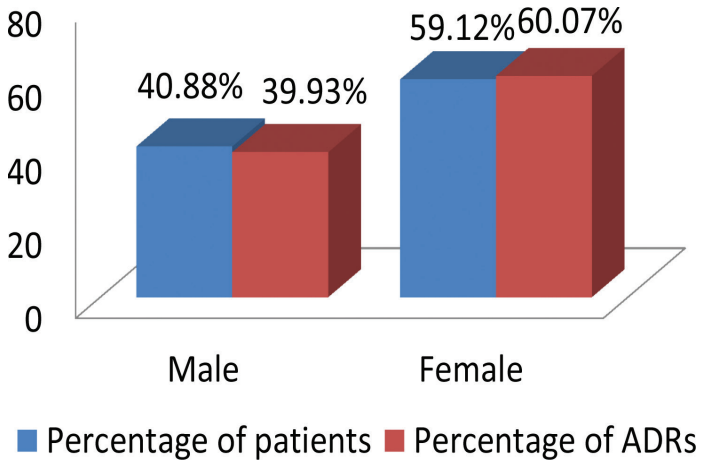


Figure 1: Gender wise distribution of ADRs

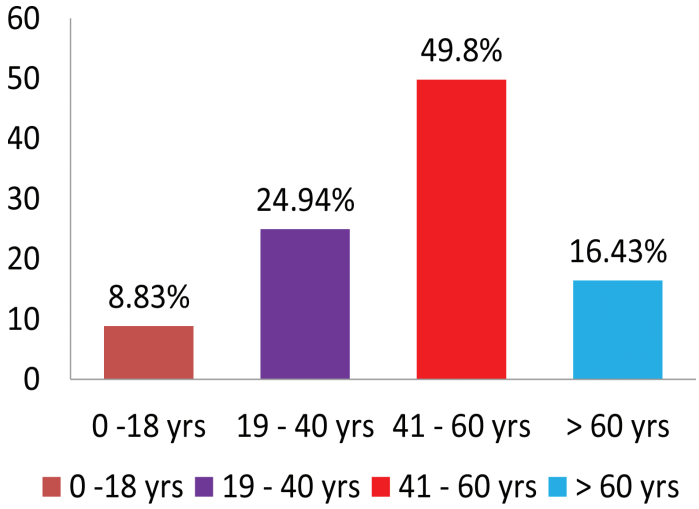


Figure 2: Age wise distribution of ADRs

Number of ADR/ADRs per patient

A total number of 2209 ADRs were collected from 1869 patients with an average of 1.18 ADRs per patient. 301 (13.63%) patients experienced two ADRs and 39 (1.77%) patients developed three ADRs. Thrombocytopenia was the most common 2nd ADR reported followed by vomiting. Similarly fever and nausea were the most common 3rd ADR observed followed by mucositis. Gemcitabine was the most common drug associated with occurrence of 2nd ADR followed by imatinib. Likewise 5-fluorouracil was responsible for most common 3rd ADR followed by imatinib and paclitaxel.

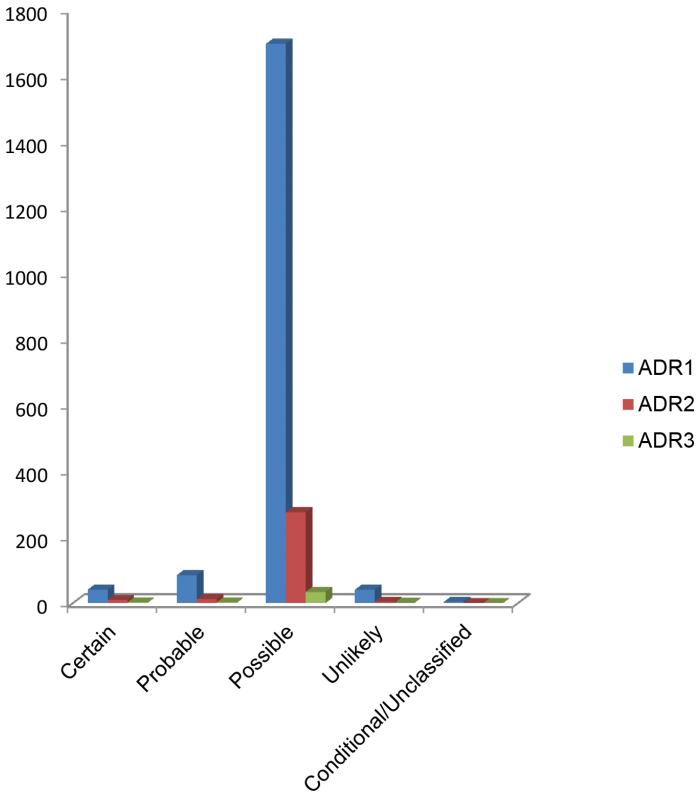


Figure 3: Causality assessment of ADRs
ADR1: First ADR experienced by the patients. ***ADR2:*** Second ADR experienced by the patients who already experienced one (first) ADR. ***ADR3:*** Third ADR experienced by the patients who experienced a total of 3 ADRs (or who already experienced first and second ADR)

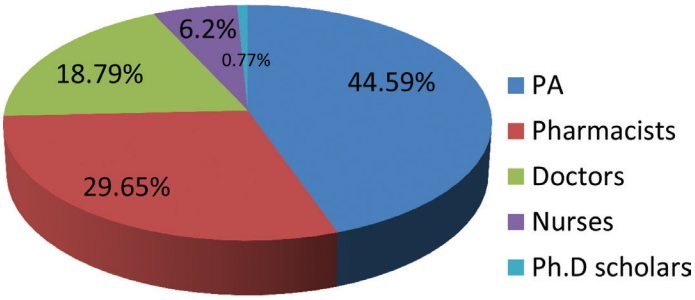
Table 3: 11 most common ADRs due to anti-cancer drugs

Sl. No.	ADR	No. of ADR	Percentage (%)
1	Anemia	280	12.68
2	Neuropathy	247	11.18
3	Neutropenia	134	6.07
4	Thrombocytopenia	126	5.7
5	Myalgia	121	5.47
6	Hand-foot syndrome	119	5.39
7	Mucositis	78	3.53
8	Vomiting	65	2.94
9	Fever	41	1.86
10	Diarrhea	39	1.77
11	Rash	38	1.72

DISCUSSION

The ADRs reported with anticancer drugs for a period of 2.5 years were collected, analyzed and reported from different departments of a multi-specialty hospital and research institute in South India. In the present study, ADRs due to anticancer drugs were observed more in females than in male patients. This may be attributed to the smaller body surface area in females. Our finding is similar to the study conducted by Sharma *et al.* [10] that showed ADRs in the age group 41-60 years were highest followed by 19-40 years and lowest in the age group 0-18 years. This finding is similar to the report of Pai *et al.*[11] who also reported mean age of patients 55.98 years and 52.96 years in male and female respectively. This could be due to the higher incidence of cancers in this age group or under reporting of ADRs in the paediatric age group.

The most common anticancer drug causing ADR was imatinib followed by docetaxel. This is in contrast to the studies showing platinum and 5-Fluorouracil as the most common anticancer drugs associated with ADRs.[12] This could be probably due to the availability of imatinib free of cost to the patients or due to the prevalence of cancer for which imatinib is a treatment option in our center.



PA : Pharmacovigilance associate

Figure 4: ADR reported by healthcare professionals

Table 4: 10 most common anti-cancer drugs causing ADRs

Sl. No.	Drug	No. of ADRs	Percentage
1	Imatinib	308	13.94
2	Docetaxel	211	9.55
3	Gemicitabine	189	8.56
4	Paclitaxel	163	7.38
5	Oxaliplatin	146	6.61
6	Capecitabine	116	5.25
7	5-FU	115	5.21
8	Vincristine	68	3.08
9	6-MP	60	2.72
10	Gefitinib	58	2.63

The most common ADR due to anticancer drug in our setting was anemia followed by neuropathy. This is similar to the study conducted by Gunaseelan *et al.* in which anemia was the most common ADR. [13] However study carried out by Mallik *et al.* reported neutropenia as the most common ADR on contrary to our finding of neutropenia as the third most commonly reported ADR.[14] According to a study by Sharma *et al.* most commonly occurring ADRs were infections (22.4%), nausea/vomiting (21.6%), febrile neutropenia (13%) and anaemia (7.2%).[10] The reason for these variations could be the non-reporting of mild ADRs like nausea and vomiting.

In our study, the most common organ system affected was blood followed by skin and appendages. This finding was related to the results of the study carried out by Mallik *et al.*[14] Contrary to this study, Chopra *et al.* found that gastrointestinal tract is the most frequently involved organ system, followed by hematological system.[12] However, gastrointestinal tract was the third most common organ system involved in our study. This may be due to the under reporting of nausea, vomiting and other mild ADRs related to gastrointestinal system in our Centre.

Most of the ADRs were reported by the technical associate followed by pharmacists and doctors. This is in contrast to the results of Kalaiselvan *et al.* that found doctors report majority of ADRs followed by pharmacists.[15] The dissimilarity of our finding could be attributed to lack of time for reporting ADRs owing to high patient load in our setting and active involvement of our Pharmacovigilance associate who is working in department of Clinical Pharmacology on a regular basis under PvPI.

Causality assessment for most of the ADR was possible as per the WHO-UMC causality assessment scale. This was similar to the study conducted by Chopra *et al.*[11] On contrary, a study conducted by Saini *et al.* had most of the ADRs as probable 97 (64.67%) followed by possible 53 (35.33%).[16]

The major limitation of the study was inability to trace the patients and the reporting personnel for additional information owing to retrospective study design.

CONCLUSION

Cancer chemotherapeutic agents have a high propensity to cause ADRs owing to their action on rapidly dividing cells. Hence early detection of these ADRs may help in minimizing the harm either by modifying the dose or changing the concerned drug with a suitable alternative. This knowledge may help in preventing the occurrence of similar reactions in future. Accordingly, an efficient adverse drug reaction monitoring centre (AMC) and reporting system is mandatory in all hospitals to generate awareness among health care professionals. Measures to promote judicious use of drugs and reduce the incidence of adverse drug reactions (ADRs) will help in promoting quality of life apart from lessening economic burden of the patients.

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CONFLICT OF INTEREST

There are no conflicts of interest.

ABBREVIATION USED

ADR: Adverse drug reaction; **AMC:** Adverse drug reaction monitoring centre; **CNS:** Central Nervous system; **HFS:** Hand foot syndrome; **GLOBOCAN:** Global burden of cancer; **PA:** Pharmacovigilance associate; **PNS:** Peripheral Nervous System; **PvPI:** Pharmacovigilance Programme of India; **RCC:** Regional Cancer Centre; **WHO:** World Health Organization; **UMC:** Uppsala Monitoring Centre.

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