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Original Article

ASSESSMENT OF PATTERN OF ADVERSE DRUG REACTIONS FROM ANTI-CANCER DRUGS IN A TERTIARY CARE HOSPITAL: A CROSS-SECTIONAL STUDY

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ABSTRACT

BACKGROUND: Chemotherapy is one of the multimodal approaches to the treatment of cancer and adverse drug reactions (ADRs) are very commonly related with these anti-cancer agents. The present study is done with the aim to assess the pattern of adverse drug reactions due to anti-cancer therapy, analyse their causality and severity, and assess the pattern of drugs used for the treatment of adverse drug reactions.

MATERIALS AND METHODS: A cross-sectional study was conducted at a tertiary care teaching hospital for one year after obtaining approval from the ethics committee. All the cancer patients of either sex with age >18 years, admitted in the oncology department were included in the study. A pre-designed proforma was used for filling demographic, clinical, and prescribing details of the patient. Causality and severity of adverse drug reactions were assessed by using the WHO-UMC causality scale and Modified Hartwig and Seigel severity scale, respectively.

RESULTS: Out of 126 cancer patients enrolled in the study, 65% were females while 35% were males. The majority (30%) of the total study participants were in the age group of 51-60 years. A total of 259 ADRs were observed in cancer patients. 83% of the total ADRs were probable/likely in causality and 74% were mild ADRs. It was observed that fatigue, weakness, and dizziness were the most commonly occurring ADRs for which multivitamins were prescribed. The most common class of drug implicated in causing ADRs was Platinum coordination complexes.

CONCLUSION: ADR monitoring is needed with anti-cancer drug management, to improve patient safety and decrease hospital stay. Management of ADRs beforehand will help in reducing the suffering of patients and increase compliance. ADR monitoring is the need of the hour especially in cancer patients in order to increase quality of life, and decrease morbidity and mortality.

KEYWORDS: ADRs, Anti-cancer agents, Pharmacovigilance, Management of ADRs, Causality, Severity.

INTRODUCTION

Cancer has become a global burden and is the leading cause of death worldwide. According to International Agency for Research on Cancer, GLOBOCAN 2020 (The global cancer observatory), Jacques Ferlay, et al. estimated in their study that there were 19.3 million new cancer cases and 10.0 million cancer deaths in the year 2020 worldwide. [(1)] Cancer is treated in many different ways like radiation therapy, hormonal therapy, biological therapy, chemotherapy, surgery, and immunotherapy. Chemotherapy is one of the multimodal approaches to the treatment of cancer. Chemotherapy regimens are very complicated and elaborate. Some frequently used classes of anti-cancer therapy are platinum coordination complexes, targeted drugs, antimetabolites, alkylating agents, etc. Chemotherapy treatment includes single and combination therapies of anti-cancer drugs, which is one of the common causes of ADR in a tertiary care hospital. As defined by World Health Organisation (WHO), adverse drug reactions are "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 the modification of physiological function". [(2)] As rightly quoted by Matthew Prior, "Cured yesterday of my disease, I died last night of my physician." [(3)] ADRs lead to increased hospital stay, increased health cost of the patient and decreased health-related quality of life of patients. Most of the time adverse drug reactions (ADRs) remain unreported. Under-reporting of ADRs caused due to chemotherapy is very commonly seen. Adverse drug reactions result in 6.5%-10.9% of hospital admissions and mortality rates of 0.15%- 2.9%. [(4)] Studies have shown that there is a high incidence and economic burden of ADR related to cancer chemotherapy. [(5)] One study from South India shows that ADRs reported in Oncology Department are the second highest percentage after general medicine. [(6)] Nausea, vomiting, weakness, fatigue, myelosuppression, mucositis, diarrhoea, neutropenia, lymphocytopenia, alopecia, etc. are some common adverse drug reactions resulting due to anti-cancer agents. ADRs occurring due to chemotherapy agents should be managed properly. Ondansetron, vitamins, growth factors, antibiotics, and corticosteroids are regularly used drug therapy for treating adverse drug reactions. World Health Organisation (WHO) defined pharmacovigilance as the

science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any drug-related problem (WHO 2002). [7] A study was done by Dipankar Chakraborty, et al has shown that pharmacovigilance is essential to detect ADRs of cancer chemotherapy to reduce morbidity and mortality. This study said that ADRs cannot be prevented but their incidence can be decreased by the timely use of various medications. [3] On that account, it becomes necessary to recognize the pattern of ADR occurring with anticancer drugs. [5] Early detection of these ADRs can reduce the economic effects and health-related effects. A study done by D. Krishnarajan, et al concluded that to increase the quality of life of patients it is necessary to identify and manage ADRs by taking appropriate measures to promote balanced and rational use of drugs. [4] The present study was done in a tertiary care hospital, with the objective to assess the pattern of adverse drug reactions from various anti-cancer drugs. This study also included treatment used for correcting these adverse drug reactions in the oncology department. Assessment of causality and severity of adverse drug reactions was also done to know the pattern of ADRs and make an effort to manage them accordingly.

MATERIALS AND METHODS

STUDY DESIGN

This study was a hospital-based cross-sectional study done for a period of one year from March 2021 to March 2022. The study was started after approval from the ethics committee. The study was conducted in the department of pharmacology and the department of medical oncology of a tertiary care teaching hospital.

INCLUSION CRITERIA:

- Age group >18 years.
- Patients of either sex.
- All cancer patients admitted to the oncology department during the study period.
- Patients on at least one anti-cancer drug.
- Patients with at least one ADR reported.

EXCLUSION CRITERIA:

- Patients who did not give informed written consent.
- Pregnant and lactating females.
- Patients whose prescriptions are not reliable and have insufficient data.
- Patients gone through only surgical treatment and radiotherapy treatment only.

SAMPLE SIZE

Cancer patients admitted to the oncology ward during the study period and fulfilling the inclusion criteria were enrolled in the study. 126 patients were studied for the present study, who had gone through 259 ADRs which are assessed in our study.

STUDY TOOLS

Patient details were taken in a pre-designed proforma, that included demographic details of the patient, clinical details of the patient, and details of drug therapy given to the patient. The WHO-UMC causality assessment criteria were used to categorize adverse drug reactions according to their causality. [7] The modified Hartwig and Seigel severity assessment scale was used to evaluate the severity of ADRs. [8]

STATISTICAL ANALYSIS

All the collected data was entered in the MS office excel worksheet and descriptive statistics was applied to assess the collected data in terms of n (%).

RESULTS

The characteristics of patients according to their demographic details are shown in Table 1. Out of 126 patients in our study, females were in majority with 65% (82) of our study population. Maximum patients were from the age group 51-60, 38 in number, and 30% of the total population. 21 patients were below the 41-age group and above 70, and 19 patients were observed.

Table 1: Demographic characteristics of the patients

VARIABLES		NUMBER	PERCENTAGE (%)
GENDER	FEMALE	82	65
	MALE	44	35
AGE	18-30	10	8
	31-40	11	9
	41-50	21	17
	51-60	38	30
	61-70	27	21
	71-80	14	11
	81-90	5	4

Figure 1 shows the pattern of adverse drug reactions. In 126 study populations, we observed, that the most commonly occurred ADRs were fatigue/weakness/joint pain which is 32% in our study, followed by nausea/vomiting which accounts for 29% of adverse drug reactions. Mucositis, hypothyroidism, hand-foot syndrome, nephrotoxicity, nerve dysfunction, renal toxicity, numbness, and stomatitis were rarely seen

ADRs, accounting for the miscellaneous group (5%) of the total study.

Figure 1: Pattern of adverse drug reactions

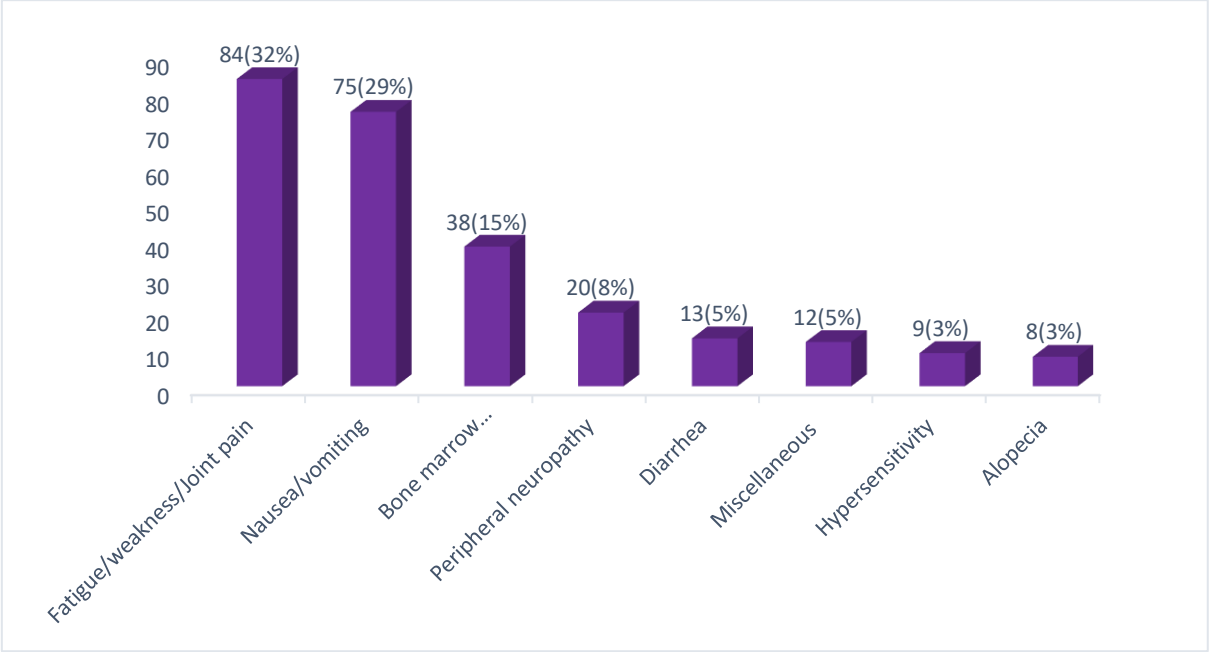

Figure 2 shows the class-wise distribution of anti-cancer therapy agents causing ADRs. Platinum coordination complex including carboplatin and cisplatin was the most common anti-cancer agent causing ADRs in the present study (26%). This was followed by targeted group drugs, antimetabolites, taxanes, alkylating agents, topoisomerase inhibitors, antibiotics, vinca alkaloids, and hormonal drugs.

Figure 2: Anti-cancer drugs implicated in causing ADRs

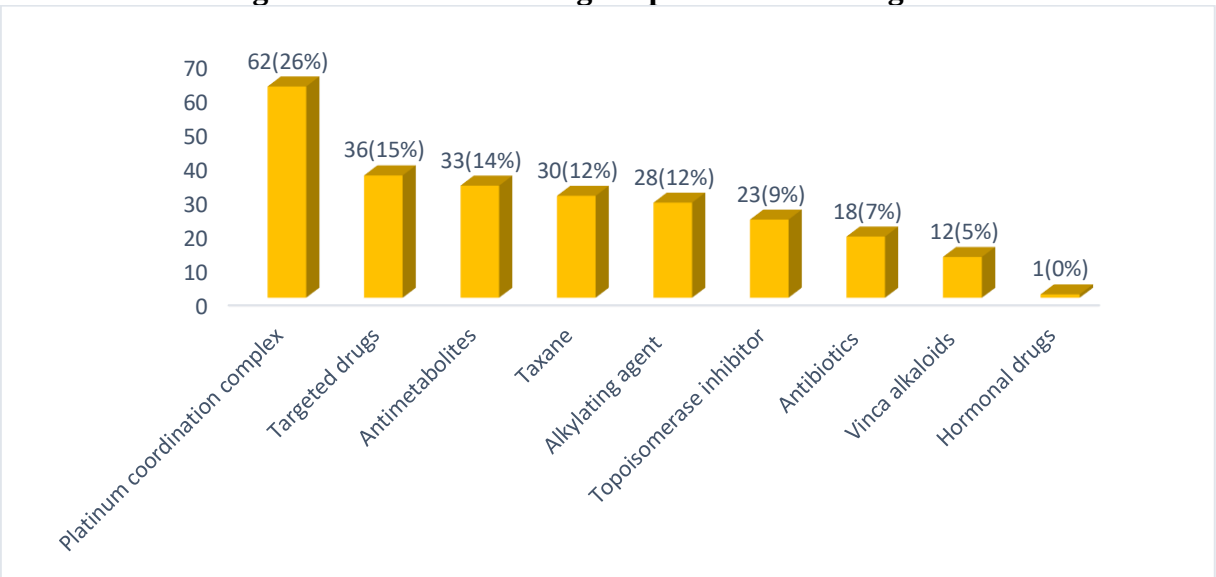

Figure 3 shows classes of drugs used for the treatment of adverse drug reactions. The most regularly used drugs in our study were multivitamins (31%) followed by ondansetron (26%). Some other drugs observed were cefoperazone, sulbactam, hydrocortisone, magnesium sulfate, and potassium chloride (7%).

Figure 3: Classes of Drugs for Management of ADRs

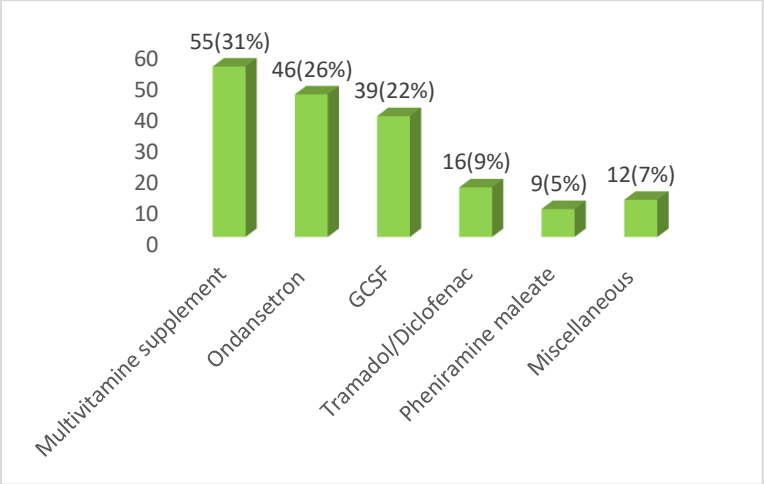

Table 2 shows the causality and severity assessment of adverse drug reactions in our study population. 206 ADRs were probable/likely in our study. There were no unlikely, conditional/unclassified, and unassessable/unclassifiable categories in the present study. 184 ADRs (74%) were mild (levels 1 and 2) followed by 65 moderate ADRs (26%). No severe ADRs were observed in our study.

Table 2: Causality and Severity of ADRs

	CATEGORIES	NUMBER OF CASES (PERCENTAGE)
CAUSALITY	Probable/Likely	206(83)
	Certain	22(9)
	Possible	19(8)
SEVERITY	Mild	184(74)
	Moderate	65(26)

DISCUSSION

ADRs due to anti-cancer drugs are of various types, which decrease patient compliance, increase hospital stays, and also increase suffering for the patient. So ADRs have to be monitored strictly and efforts should be made to minimize these ADRs. Based on the FDA (Food and Drug Administration) Adverse Event Reporting System (AERS), women encounter more ADRs as compared to men, reasons for this are various pharmacodynamic or pharmacokinetic factors, polypharmacy, or differences in reporting patterns of ADRs. [9] In the present study we have observed that females are more prone to adverse drug reactions from anti-cancer drugs as compared to men, with 65% seen in females. Studies done by Priya Saji Koliyakodu et al. and Krishnarajan et al. also showed female preponderance of adverse drug reactions. [10,4] Some studies give results that are in contrast with our study, with male preponderance, for example, studies done by Ramasubbu et al. and Julie Birdie Wahlang et al. [11, 12]

Our study has seen that the majority of ADRs are present in the age group 51-60 years. Out of 126 patients in our study, 30% i.e., 38 patients are of the age group between 51-60 years. These results are the same as studies done by Rout A et al. and Prasad A et al. [13,14] We have also seen that after 51-60 age group next majority come in between the ages 61-70 with 21% ADRs, followed by 41-50 age group, with 17% ADRs. Some studies show 41-50 years age group patients have more ADRs as compared to other age groups, these studies are done by Chakraborty, et al. and Chopra, et al. [3, 15]

The most common class of anti-cancer drugs causing ADR in our study was platinum coordination complex with carboplatin the most common drug used followed by cisplatin. This is similar to the study done by Guduru H et al., which shows carboplatin and paclitaxel to be the most common drugs. [16] There are most studies showing cisplatin to be the most common drug causing ADR, some of these studies are done by Ramasubbu, et

al., Chakraborty, et al., and Chopra, et al. [11, 3, 15] A study was done by Aghamohammadi, et al. 5-Fluorouracil to be the most common drug causing ADRs. [17]

The next most common class of drug-causing ADRs after the platinum group are targeted class drugs with 15% results in the present study. After carboplatin and cisplatin, other anticancer drugs causing ADRs are etoposide, rituximab, and doxorubicin.

The most frequent ADR from carboplatin is fatigue/joint pain and that from cisplatin is nausea/vomiting in our study. Similarly, a study done by Chopra, et al. has shown nausea and vomiting to be the most common ADRs from cisplatin therapy. [15] On the contrary, a study done by Chakraborty, et al. has said that anorexia, constipation, anemia, leukemia, and weakness, are the most continuously observed ADRs in patients treated with cisplatin therapy. [3]

We have seen that weakness/fatigue/joint pain/body pain are the most common ADRs in our study region, which is similar to the results of the study done by Aghamohammadi, et al. [17] Out of 259 ADRs in our study, 84 which is 32% are fatigue/weakness. A study done by Krishnarajan, et al. has shown nausea and vomiting to be the most common ADR occurring due to anti-cancer drugs. [4] Nausea and vomiting are the second commonest in our study, which are 29% of 259 ADRs. Alopecia followed by anorexia, nausea, and vomiting are the ADRs shown by Chakraborty, et al. in their study. [3] Other ADRs frequently seen in the present study are bone marrow depression, myelosuppression, peripheral neuropathy, and some cases of hypersensitivity are also observed.

In the present study, repeatedly used drugs for the treatment of adverse drug reactions are ondansetron, multivitamin supplements, granulocyte colony-stimulating factor (G-CSF), tramadol followed by corticosteroids, pheniramine, antibiotics, calcium, and other ions. Ondansetron is mainly prescribed to relieve nausea and vomiting caused by cancer chemotherapy drugs. Bone marrow suppression including neutropenia, thrombocytopenia, or anemia is mainly corrected by growth factor support (GCSF), similar results are shown by Ramasubbu et al. in their study. [11] Multivitamins are used most frequently for the treatment of weakness/fatigue/dizziness. These are the most commonly used drugs in our study.

The causality pattern of ADRs in the present study is calculated by the WHO-UMC causality scale. Most of the ADRs in our study came out to be probable/likely, which is 83% of all ADRs. A study done by Amartya De, et al. also shows the same results with the majority of probable ADRs. On the contrary, a study done by Chakraborty, et al. and Chopra, et al. has maximum 'possible' category ADRs. [18, 3, 15]

The severity pattern of ADRs is 74% mild followed by 26% moderate in the present study. The severity pattern is checked using the modified Hartwig and Seigel scale. Chakraborty, et al., Wahlang JB, et al., and Chopra, et al. also showed the same results in their studies with maximum ADRs being in the mild category. [3,12,15]

Thus, the present study wants to draw the attention of medical professionals towards the ADRs occurring due to anti-cancer agents and emphasize on pharmacovigilance studies, which will help to study more and more ADRs, and treat them beforehand or try to reduce them, to improve the outcome of chemotherapy treatment in cancer patients.

CONCLUSION

Anti-cancer therapy agents are one of the common causes of ADRs in a tertiary care hospital. Females are more prone to ADRs and the age group in which maximum ADRs are observed is 51-60 years. The most frequently occurring ADRs in this study were weakness/fatigue. Platinum group of anti-cancer drugs are causing the majority of ADRs with multivitamins and ondansetron most commonly used drugs for the treatment of ADRs. This study concludes that pharmacovigilance is an essential tool needed with anti-cancer therapy, as polypharmacy is a very common practice in cancer patients and a variety of reactions from mild to severe occur due to these agents. ADRs should be monitored more precisely and try to prevent them in advance by giving the correct medications.

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

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