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Original Research Article

Pattern of adverse drug reactions to anticancer drugs at an apex hospital in south India: A retrospective study

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ABSTRACT

Cancer chemotherapy is rampant as cancer is the 2nd most common cause of global mortality. It is challenged by a horde of adverse drug reactions (ADRs) and adverse events. A proper study of these ADRs is very crucial to limit their occurrences and thereby ameliorate the sufferings of the patients. Our study was to assess the frequency, nature and profile of the ADRs with anticancer drugs. A retrospective analysis of the ADR data collected over a period of 5 years was considered. Demography, drug related changes and clinical details of the patients were recorded and analysed. A total of 1145 ADR events were reported during the study period of January 01, 2017 to December 31st 2021 of which 232 cases (20.26 %) were due to anticancer drugs. The majority of the ADRs were accounted in females and in the elderly age group (>60 years). The commonly reported ADRs included breathing difficulty, chest discomfort, itching all over the body, numbness, neuropathy, mucositis and hand foot syndrome. The most common drugs that caused ADRs were Platinum coordination complex drugs, Taxanes, Rituximab and pyrimidine antagonists like Capecitabine and Gemcitabine. Causality assessment done using WHO-Uppsala Monitoring Centre causality assessment scale which showed 69.4% cases as "probable", 29.3% cases as "possible" and 1.3% as "certain". Severity assessed using the modified Hartwig and Siegel scale showed most of the cases as of moderate severity. Most of the ADR events in our study was manageable although a few required the withdrawal of the causative drug. Rigorous monitoring and adequate reporting are very crucial for the prompt identification, assessment and timely management of ADRs in the patients receiving chemotherapy so as to improve the quality of life in these patients.

1. Introduction

Cancer is known to be one of the three leading causes of death in the modern world. Approximately 12% of deaths that occur annually worldwide are due to cancer.[1] The prevalence of cancer in India is estimated to be 2.5 million and the incidence of cancer is about 70-90 per 100,000 persons.[2] Anticancer therapy has undergone various breakthroughs in the past decades and is one of the priority research areas. The antineoplastic drugs range from the cell cycle-specific and non-specific drugs to the molecularly targeted agents and the most recent immunotherapy drugs. However, despite these advancements, cancer continues to be one of the leading causes of mortality and morbidity worldwide. Most of these anticancer drugs have a narrow therapeutic index and play a significant role in contributing to the global burden of adverse drug reactions. The World Health Organization (WHO) defines adverse drug reaction (ADR) as "A response to a drug, which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or the modifications of physiological function."[3]

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The Pharmacovigilance Programme of India (PvPI) plays a key role in addressing the ADRs and thereby instituting remedial policy change. Patients who receive chemotherapy are susceptible to a wide range of ADRs as they receive multiple drugs as a part of their regimen which in turn cause an increase in morbidity and mortality. Newer advances in antineoplastic drugs are also associated with a diversity of adverse reactions. It is mainly during the post-marketing phase that a large number of newer ADRs are noted. By the time a drug is marketed, only about 1500 patients may have been exposed to the drug. Thus, only those ADRs which occur at a frequency greater than 1 in 500 would have been identified at the time of licensing[4] There is a dearth of pharmacovigilance data pertaining to anticancer drugs despite their high potential for drug toxicity.[5] These ADRs that are associated with the antineoplastic drugs hamper the effectiveness of the treatment making the otherwise suffering patient endure even more. So, if detailed studies regarding the ADRs of these drugs are done, it can prove to be a helping hand for the oncologists to broaden their knowledge regarding these drugs and thereby be more discerning in choosing the ideal regimen that will have a low impact on the patient's health and quality of life. Accordingly, adequate identification and reporting of ADRs help to recognize the risks associated with the treatment and to promptly intervene and ameliorate these adverse effects. This study was conducted to analyse the ADR profiles of anticancer drugs in patients attending the oncology department of a tertiary care institution. All these ADRs were reported to the regional training centre-adverse reaction monitoring centre (RTC-AMC) established under PvPI.

2. Materials and Methods

The study was conducted in accordance with the Pharmacovigilance Programme of India (PvPI) using data obtained from Adverse Drug Reaction monitoring centre at a tertiary care teaching hospital in South India. It was a retrospective study, and the data was obtained from the filled ADR forms received by the pharmacovigilance regional training centre of the institute. An observational analysis was done among the ADR data reported from January 01, 2017 to December 31, 2021.Data reporting was voluntary and can be reported by a physician, pharmacist, nurse or any Health care professional (HCP) who recognizes the ADR event.

The demographic details of the patients were recorded. Details regarding the occurrence and type of ADR, suspected drug, dosage, diagnosis, organ system affected, management principle, action taken, outcome and the ADR reporter were collected and recorded in the excel sheet and statistical analysis was made therefrom. The reported ADRs were assessed for causality using the causality assessment scale proposed by the WHO Collaborating Centre for International Drug Monitoring – the Uppsala Monitoring Centre which classifies the suspected ADRs as certain, probable, possible, unlikely, conditional/unclassified and un-assessable/unclassifiable. The severity of the reported reactions was assessed using a modified Hartwig and Siegel scale.

3. Results

A total of 1145 ADR events were reported during the study period of January 01, 2017 to December 31st 2021 of which 232 cases (20.26 %) were due to anticancer drugs. The ADRs were categorised into 9 groups based on the organ system that got affected. In some patients, more than one ADR was reported. The majority of the ADRs were accounted for in females (n = 154, 66.4%). The male: female ratio in the current study was 1:50. A vast proportion (71%) of the ADRs were found to be in the age group 51-80 years, 27% in 19-50 years and 2% in the age below 18 years. Platinum coordination complex drugs, Taxanes, Rituximab and pyrimidine antagonist drugs were the most common drugs found to be causing the ADRs. Causality assessment was done by the WHO causality assessment scale which showed that 69.4% of cases were "probable", 29.3% of cases as "possible" and 1.3% as "certain". The reported reactions were assessed for severity using the modified Hartwig and Siegel scale and most of the ADRs were categorised as of moderate severity. On analysing the outcome of the ADR, a major proportion (76.7%) of the patients recovered while the remaining (23.3%) were in recovering phase.

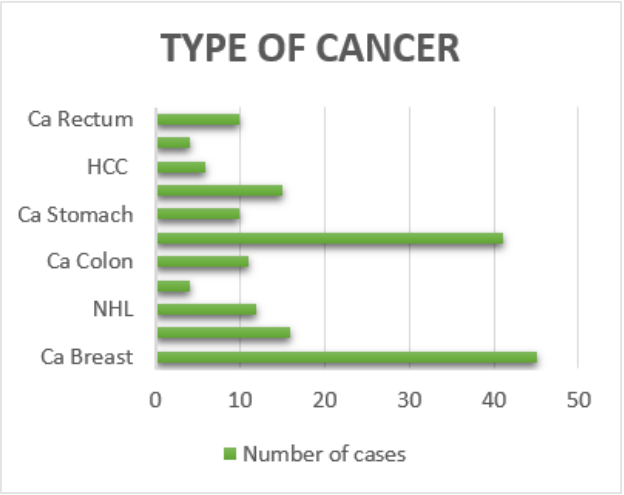

Fig. 1: Type of cancer

4. Discussion

Cancer treatment in the present era is a multimodal approach which includes chemotherapy, radiotherapy,

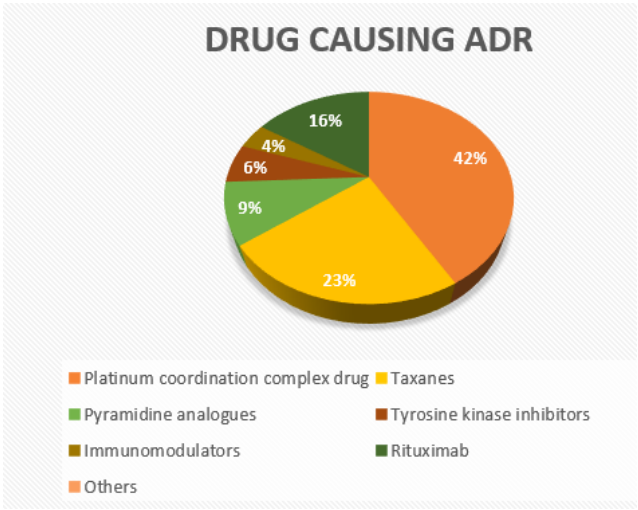

Fig. 2: Drug causing ADR

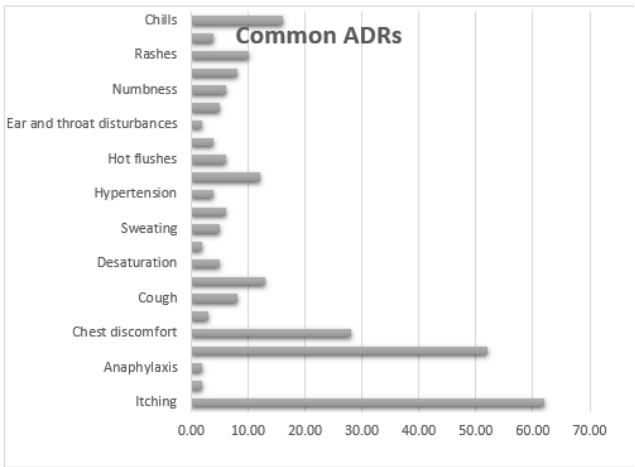

Fig. 3: Common ADRs

Table 1: Organ / systems involved

S. No	Organ system involved	Number of cases	Percentage
1	CNS	14	4.9%
2	CVS	8	2.8%
3	RS	71	24.8%
4	Skin & appendages	88	30.8%
5	ENT	4	1.4%
6	GIT	19	6.6%
7	General	66	23.1%
8	Haematology	14	4.9%
9	Ocular	2	0.7%

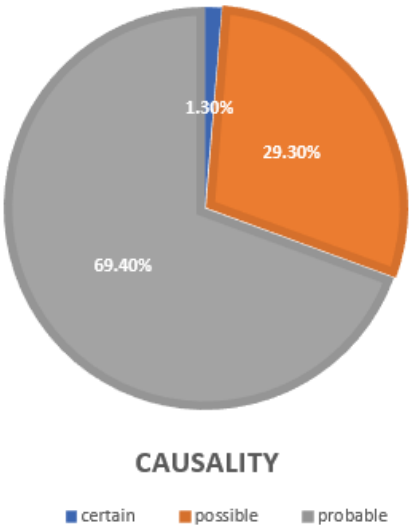

Fig. 4: Causality

surgery, hormonal, immunological and biological therapy. Over the past few years, cancer chemotherapy has been revolutionized with the discovery of newer antineoplastic drugs but simultaneously with the appearance of newer adverse effects by default. The prompt identification, reporting and documentation of these ADRs play a very crucial role in improving the quality of life of the patients and thereby ameliorating the morbidities associated with it. This can only be achieved by a rigorous drug safety monitoring and pharmacovigilance program.

The UN population prospects show that, as of 2021, 50.24% of the world population constitutes males, while 49.58% of the world is represented by the female population.[6] According to the National Cancer Institute, the rate of new cases of cancer among men was 489.2 per 100,000 men per year and for women was 425.6 per 100,000 women per year[7] The demographic profile of our study showed that most of the adverse effects were found in females (66.4%) when compared to males (33.6%). This is consistent with the studies conducted by Chopra *et al.*, (2016) in which the presence of ADRs in females was more than twice in comparison with males.[8] This might be due to the gender-wise differences in drug pharmacokinetics and pharmacodynamics[9] or due to the hormonal changes that occur in females during the various stages of life which can lead to an alteration in the pharmacokinetics of the drugs.[10]

The ADRs were found to be more among the elderly (age >50 years) as was found in a similar study which showed that the ADRs were significantly higher in the elderly when compared to other age groups.[11] This should urge the clinician to be cautious while prescribing anticancer drugs to the elderly.

The majority of the ADRs occurred during the inflow of the drug (55.6%), a few occurred after the complete

administration of the drug (21.5%) while others occurred late (22.8%).

The most common cancers that were encountered in our study includes carcinoma breast (n = 45, 19.4 %), followed by carcinoma ovary (n=38, 16.4%), carcinoma lung (n=15, 6.5%), non-Hodgkin's lymphoma (n=12, 5.2%), carcinoma colon (n=11, 4.7%), carcinoma stomach and carcinoma rectum (n=10, 4.3%). [Figure 1]

Among the chemotherapeutic agents prescribed, platinum compounds (carboplatin, oxaliplatin and cisplatin) accounted for most of the ADRs (n=84, 36.2%), followed by taxanes (Docetaxel & Paclitaxel) which caused about 20.25% of the ADRs. These findings were similar to the studies conducted by Kaur, *et al.*, (2015)[12] and Mallik, *et al.*,(2015)[13] who also reported that the alkylating agents like platinum coordination complexes, antimetabolites and taxanes were the chief ADR causing agents. In our study the CD20 Inhibitor drug Rituximab was the next major culprit which accounted for about 13.8% of the ADRs. The other drugs which contributed to ADRs includes the pyrimidine analogue antimetabolites (Gemcitabine and Capecitabine), Tyrosine kinase inhibitor drugs (Imatinib, Lenvatinib, Sorafenib, Regorafenib) and the immunomodulator drugs (lenalidomide and thalidomide). [Figure 2]

We noticed from our study that the most common ADRs that were encountered were breathing difficulty, chest discomfort, itching all over the body, numbness, neuropathy, mucositis and hand-foot syndrome and the commonest rescue drugs for these ADRs was Inj. Hydrocortisone and Inj. Chlorpheniramine maleate. These were the ADRs other than nausea, vomiting and alopecia which are the common accompaniments of anti-cancer drugs. [Figure 3]. The most common organ system that was afflicted by the adverse reaction following anticancer therapy was skin and appendages (30.8%), followed by the respiratory system (24.8%). [Table 1] It was noted from our study that while most of the ADRs led to the withdrawal of the suspected drug, an equal number of cases also led to the infusion with the suspected drug to be restarted and continued (n=110, 47.41%). In a smaller proportion of the cases the dose of the suspected drug was reduced (n=9, 3.8%) and in a mere 1.9%, cases the offending drug had to be replaced with another anti-neoplastic agent.

When causality was evaluated using the WHO-UMC causality assessment scale, it was found that most of the ADRs (69.4%) were under the "probable" category and 29.3% of cases were under the "possible" category. Only a minute fraction of 1.3% of cases fell under the category of "certain" cause of ADR. These findings paralleled a study by Amartya De which reported maximum cases as "probable", a minority as "possible" and very few cases as "certain" causes of ADRs.[14] However, in contrast to our study, Chakraborty in his study reported maximum cases under the "possible" category and only a minority under "probable" category.[15] [Figure 4]

Severity assessment was done using a modified Hartwig and Siegel scale in our study, which revealed that about 51.7% of cases were moderate while 48.3% of cases were mild in severity. On analysing the outcome of the ADR, a major proportion (76.7%) of the patients recovered while the remaining (23.3%) were in recovering phase. This is because of the effectiveness of prompt institution of rescue medication. When the 5 yearly reporting of ADRs was analysed, a significant curtailment in the reporting was detected. This can be due to under-reporting of cases. The toxicity of the traditional chemotherapeutic drugs is very much familiar to most people and thereby these toxicities masquerade themselves as normally expected effects of the drug. This leads to the under-reporting of the ADRs which is evident from this study as none of the classical adverse effects of cancer chemotherapy such as alopecia, fatigue, nausea and vomiting etc have been reported. Under reporting appears to be positively selective, as only the most commonly known effects of cancer chemotherapy and the less severe ones have been not reported.[16] This might be due to the fact that healthcare workers only prefer to report those ADRs that are unexpected from the suspected drug and the ones which were preventable rather than reporting the adverse effects which are already been described in the literature and the ones which are nonpreventable and predictable as found in a study conducted by Hohl *et al.*[17]

We noted that most of the ADRs (60.34%) were reported by the nurses, 26.7% ADRs were reported by the clinical pharmacist and 11.7% cases by the Physician assistants. Only a mere 1.23% of cases were being reported by the doctors! This can be due to various reasons including the lack of knowledge and awareness about Pharmacovigilance Programme of India (PvPI), lethargy, insecurity, complacency, workload and lack of training as observed in other similar studies.[18] Low level of knowledge about ADRs and pharmacovigilance concept proves to be one of the major factors in the under-reporting of ADRs.[19]

Cancer chemotherapy is itself a costly preposition and the presence of these ADRs increases the economic burden on the patients. We aimed to look for any probable predictors of these adverse reactions but there seem to be no predictors and hence we are stumped to resolve this issue. The limitation of this study was that it's a single centre-based study and was retrospective in nature.

The recommendations from our study include increased ADR reporting from Oncology, complete ADR filled forms with a detailed description of the ADRs and their management and the details of the consequences of the ADRs to be filled in the ADR form.

5. Conclusion

ADRs due to antineoplastic drugs are inevitable and a cause for major concern among cancer patients. Most of

the ADR events in our study were manageable although a few required the withdrawal of the causative drug. Rigorous monitoring and prompt identification are very crucial for the, assessment, timely management and adequate reporting of ADRs in the patients receiving chemotherapy to improve the quality of life in these patients.

6. Acknowledgement

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7. Source of Funding

None.

8. Conflict of Interest

None.

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