Original Article

Frequency, nature, severity and preventability of adverse drug reactions arising from cancer chemotherapy in a teaching hospital

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Abstract

Background: An adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as "Any response to a drug which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy". Cancer chemotherapy is associated with the occurrence of ADRs, which is a worldwide problem. Monitoring and reporting of these ADRs are essential to safeguard the patient and to manage it accordingly. The outcome would create alertness and prevent their recurrence. Hence, we have undertaken a hospital-based study to study the frequency and nature of ADRs due to chemotherapeutic agents. **Methods:** A total of 500 patients developed ADRs due to cancer chemotherapy from 13th April 2018 to 18th September 2019. Demographics of the patient, drugs taken, and ADRs encountered were recorded in a predesigned form. **Results:** A total of 665 ADRs were recorded from 500 patients. Anemia was the most common ADR encountered followed by nausea/vomiting and leucopenia. Leukemia (s) were common cancer observed followed by lung and breast cancers. The most common drugs implicated were cisplatin, paclitaxel, carboplatin, and doxorubicin. Naranjo's scale showed 92% of ADRs as probable and 7% as possible. Severity scale showed 80.2% of ADRs were of moderate (level 3 and 4) severity, 11.6% of mild (level 1 and 2) severity, and 8.2% of level 5 severity. A total of 26.8% of ADRs were deemed preventable and 73.2% were not preventable. **Conclusions:** Our study provides safety data regarding the usage of anti-cancer drugs. Hence, it creates alertness among the treating doctors to prevent its recurrence.

Keywords: ADRs, cancer chemotherapy, India, preventability, severity, teaching hospital

Introduction

Cancer has become a global burden and is one of the major causes of mortality in developing countries and the incidence of the disease is drastically escalating every year in these countries.[1] Due to rapid globalization and insalubrious lifestyles and the acceptance of many features of a western dietary pattern, there is a higher occurrence of cancer in developing countries.[2] For the management of cancer, various treatment options including surgical removal, radiotherapy, chemotherapy, and immunotherapy have been made available and the choice of treatment happens to be dictated by the site of the tumor, stage of the disease, and the general condition of the patient.[3,4]

An adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as "Any response to a drug which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy".[5] ADRs of cancer

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chemotherapy have considerable economic as well as clinical repercussions as they often lead to hospitalization, prolongation of hospital stay and emergency hospital visits.

Antineoplastic agents are highly beneficial in oncological therapeutics, still, they are used with vigilance in view of considerable toxicity and narrow therapeutic window.[6] Newer drugs are being introduced into the market after accelerated approval. With a continued increase in the number of antineoplastic agents used for cancers, the spectrum of ADRs associated with them has also become more diverse. During clinical trials, due to a limited number of study subjects, only commonly observed ADRs are reported. However, in the post marketing phase, more ADRs are unmasked. The primary care physicians play a role in helping the patients' with treatment options, providing psychological support, managing comorbid conditions, and recognizing and managing the complications of cancer as well as ADRs arising from cancer chemotherapy. ADRs like nausea and vomiting can be easily managed by primary care physicians.

There have been no previous studies conducted in the Uttarakhand area to systematically explore the safety profile of anticancer drug use. Hence, the objective of our study was to generate baseline data and analyze the ADRs in the Uttarakhand region and associated hilly areas that constitute a heterogenous population group.

Materials and Methods

Study design and setting

This study was a prospective observational study conducted from April 13, 2018 to September 18, 2019 in patients who received cancer chemotherapy after obtaining approval from the Institutional Ethics Committee (AIIMS/IEC/18/161 dated 4.1.2018). The study was conducted in the Departments of Radiotherapy and Hemato-Oncology, AIIMS Rishikesh. The data was captured from inpatients as well as outpatients of both the departments and also from the daycare ward.

Study population

Cancer patients who received cancer chemotherapy in the Departments of Radiotherapy and Haemato-Oncology, AIIMS Rishikesh and developed ADRs were included in the study.

Inclusion criteria

1. Newly diagnosed patients of hematological and non-hematological malignancies who received cancer chemotherapy.
2. Patients receiving any chemotherapy including cytotoxic drugs and biological agents and who developed at least one ADR.

Exclusion criteria

Patients who were unwilling to give informed consent for this study.

Data collection

Data regarding ADRs were recorded from the patients and their medical records using standard data collection format.

Anatomic Therapeutic Chemical (ATC) Classification system codes of the WHO Collaborating Centre for Drug Statistics Methodology was applied as appropriate for therapeutic drug categories.[7]

Study tools

Specialized case record forms were used for extracting data regarding the patient's demographic profile and details of drugs received during a chemotherapy session.

The causality of ADRs due to suspected medication (s) was assessed using the Naranjo's Causality Assessment Scale.[8] The Naranjo's Algorithm, a questionnaire designed by Naranjo *et al.*, which contains 10 objective questions with three types of responses – yes, no, or do not know.

The severity of the ADRs was assessed using Modified Hartwig and Siegel Severity Scale,[9] which classifies ADRs into mild (levels 1 and 2), moderate (levels 3 and 4), and severe (level 5). Preventability assessment of the ADRs was done by using Schumock and Thornton Scale,[10] which classifies the ADRs into preventable (probably and definitely preventable) and not preventable.

Statistical analysis

All data were analyzed with the help of Statistical Package for the Social Sciences (SPSS) version 20.0. Descriptive data are represented as percentages and frequencies.

Results

Demographic pattern of patients

Table 1 describes the demographic parameters of our study participants. A total of 500 patients developed ADRs during the study period, among which 306 (61.2%) were males and 194 (38.8%) were females. The mean age of the study population was 47.12 ± 18.324 years.

Nature of ADRs with suspected drugs

Figure 1 shows the pattern of ADRs recorded. In our study, a sum of 665 ADRs was recorded and analyzed from 500 patients. Most of the cancer patients who developed ADRs during chemotherapy (233 (46.6%)) were found to be between the age group of 41 to 60. Among the ADRs encountered, the most common were anemia (32.4%) followed by nausea and vomiting (20.6%). Leucopenia (15.8%), neutropenia (3.6%), and thrombocytopenia (11%) were the other hematological ADRs observed in our study. Rashes were reported in 5.6% of patients, with consequent symptoms and signs of peripheral neuropathy in 5.2%, headache in 5.0%, and fever in 4.4%.

Analysis of various types of cancers and drugs which are implicated

Figure 2 depicts the various types of cancers observed in our population. Leukemia (s) were the most commonly observed cancer in this setup, which accounts for 16.4% followed by lung cancer in 13.4%. Leukemia (s) constitute acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, and acute promyelocytic leukemia.

Table 2 outlines the distribution of drugs that are implicated in ADRs. The most common drugs which have caused ADRs were cisplatin (24.6%) followed by paclitaxel (17.4%). Carboplatin was found to be the third most frequent antineoplastic medication, which caused ADRs followed by doxorubicin and cyclophosphamide.

Table 1: Demographic characteristics of cancer patients (*n*=500)

Variables	Frequency (*n*)	Percentage (%)
Gender		
Male	306	61.2
Female	194	38.8
Age in Years		
0-18	50	10
19-40	91	18.2
41-60	233	46.6
>60	126	25.2
Education		
Illiterate	136	27.2
Primary/secondary	275	55
Collegiate	89	17.8
Occupation		
Business/Agriculture	137	27.4
Housewife	103	20.3
Government employees	47	9.3
Private employees	110	21.7
Unemployed	103	20.3

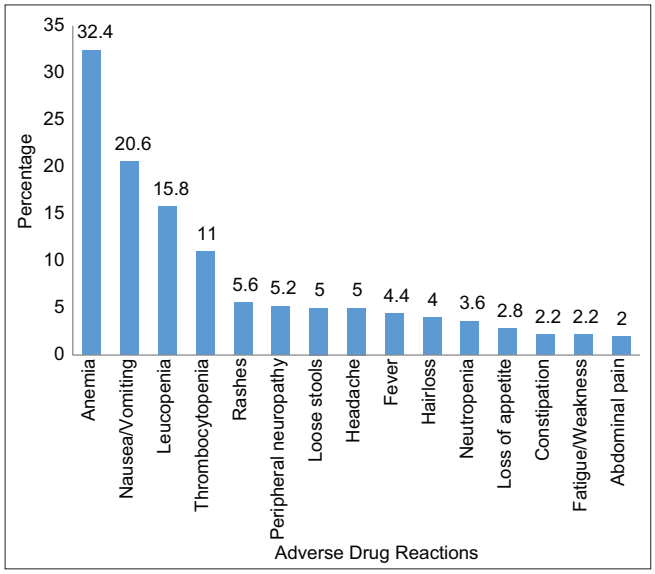

Figure 1: Pattern of Adverse Drug Reactions

Causality, severity, and preventability assessment

Naranjo causality assessment scale showed that 91.6 % of ADRs were probable, whereas 7.2% and 1.2% of ADRs were deemed possible and definite, respectively. Modified Hartwig and Siegel Severity Scale showed that 11.6% of ADRs were mild (level 1 and 2), 80.2% of ADRs were moderate (levels 3 and 4) and 8.2% of ADRs were of level 5 severity. Preventability assessment with Schumock and Thornton Scale showed that 26.8% of ADRs were preventable, out of which 13.2% were definitely preventable and 13.6% were probably preventable. As per this scale, 73.2% of ADRs were not preventable [Figures 3-5].

Discussion

After the ADRs were recorded and analyzed, it was found that the population with a mean age group of 47.12 ± 18.32 years was the one highly susceptible to the development of ADRs. The occurrence of ADRs was high in male participants (61.2%) as compared with their female counterparts (38.8%). This finding is consistent with other studies.[11,12] However, few studies show that females have a higher incidence of ADRs.[13,14]

Patients aged between 41–60 years encountered most of the ADRs, which accounts for 46.6% followed by those aged > 60 years (25.2%). It was found that the frequency of ADRs was higher in old aged patients in other studies.[15,16] The possible explanation could be that the metabolizing capacity of the liver and the renal excretory functions are generally compromised in old age leading to building up of drug levels in the body thereby raising the possibility of ADRs.

The most common malignancy in our setting was leukemia (s) followed by lung cancer and breast cancer. These findings are similar to a study conducted by Gunaseelan *et al.*, 2014.[17] A similar study by Mrugank and Hareesha, 2013 observed that gastrointestinal and breast cancers were more commonly associated with ADRs.[18] Another study showed that patients afflicted with lung cancer and breast cancer encountered ADRs

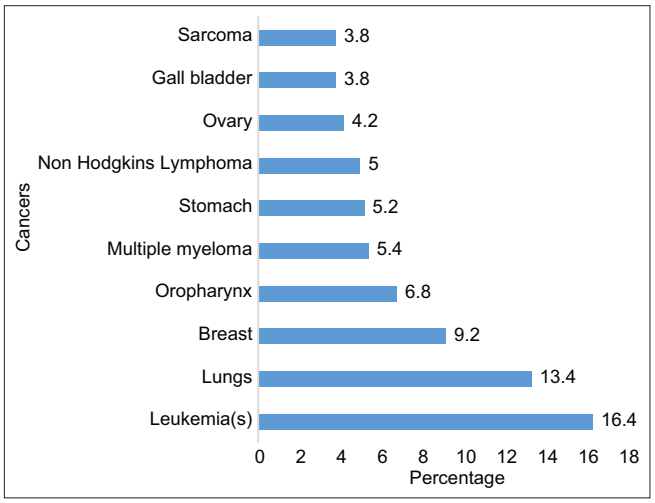

Figure 2: Various cancer types observed in our study population

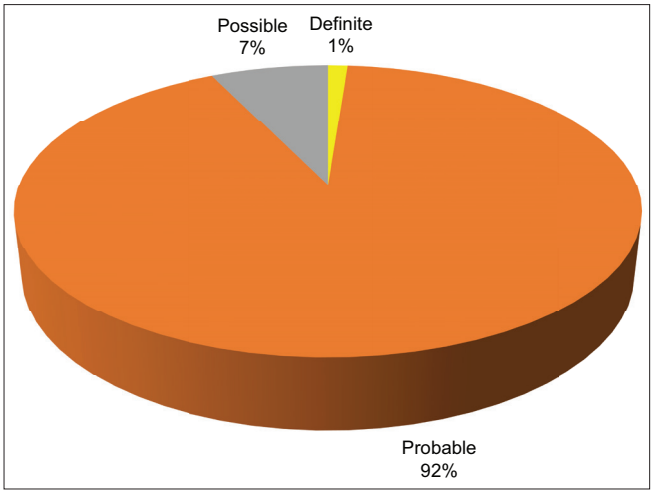

Figure 3: Naranjo's causality assessment scale

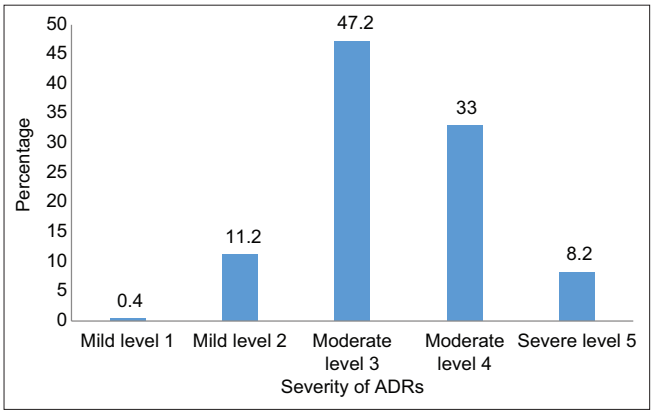

Figure 4: Modified Hartwig and Siegel severity assessment scale

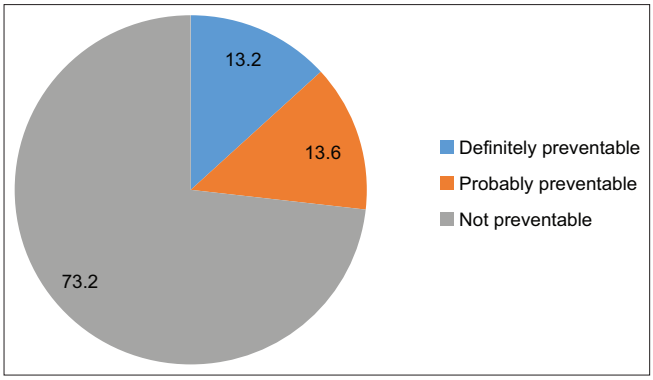

Figure 5: Schumock and Thornton preventability assessment scale

more frequently.[12] The probable explanation for these variations may be due to differences in the topographical distribution and hereditary makeup of the populations.

The most common anti-neoplastic drug causing ADR was cisplatin followed by paclitaxel in our study population which is comparable with other research reports.[14,19] The most common ADR encountered in our study population was anemia. This finding is consistent with a study conducted by Gunaseelan *et al.*, 2014.[17] A recent study by Aghamohammadi *et al.* showed that body pain was the most common ADR.[20] Some other studies have highlighted nausea and vomiting as the commonest ADRs.[12,21] In our study, nausea and vomiting were the second-most common ADRs. Cytotoxic chemotherapy drugs suppress hematopoiesis, and also damage the rapidly proliferating cells of marrow leading to myelosuppression.

A total of 20.6% of patients developed nausea and vomiting in our study subjects, which is similar to a study conducted by Lavan *et al.* 2019.[22] The incidence is lower when compared with 31.5% and 48.1% that was unraveled in two other studies conducted by Amartya, 2010 and Kirthi *et al.* 2014,[23,24] respectively. The curtailed incidence of nausea and vomiting in our study population may possibly be due to preemptive premedication with drugs such as ondansetron, and judicial use of ranitidine, pantoprazole, dexamethasone, and aprepitant. The treatment plan in our hospital for chemotherapy-induced nausea and vomiting was the administration of higher doses of palonosetron or granisetron and aprepitant, which is in accordance with reports of a study, where patients were given large doses of antiemetic drugs to treat nausea and vomiting due to cancer chemotherapy.[13]

From our study, we found that leucopenia and neutropenia were observed in 15.8% and 3.6% of patients, respectively. In our setting, neutropenic patients experienced life-threatening bacterial infections and were treated with appropriate antibiotics as per the evidence from culture and sensitivity reports. To overcome leukopenia and neutropenia, patients were treated with filgrastim (granulocyte colony-stimulating factor (G-CSF)). Thrombocytopenia was observed in 11% of patients in our study population, diagnosed by observing low platelet counts, such patients were managed with platelet transfusions when indicated.

Peripheral neuropathy is a challenging clinical problem for patients receiving cancer chemotherapy. In our study population, it was found that bortezomib (a 26 S proteasome inhibitor) was the most common drug responsible for neuropathy followed by paclitaxel and vincristine. The neuropathy associated with bortezomib treatment evolves as a predominant sensory axonal polyneuropathy. One hypothesis is that bortezomib damages the satellite dorsal root ganglion (DRG) and Schwann cells.[25] Case reports regarding bortezomib-induced peripheral neuropathy are available in the literature.[26,27] The underlying cellular pathway for bortezomib-induced polyneuropathy is nebulous. Other likely explanations would include its targeted activity at the level of mitochondria. This precipitates apoptosis, which then affects not only the cancer cell but also the neurons. Another explanation includes the blockage of NF-kB activation which in turn would inhibit nerve growth factors required for neuronal survival.[27] In our setting, patients with chemotherapy-induced peripheral neuropathy were treated with gabapentin, pregabalin or amitriptyline, which is similar to a study by Grammatico *et al.* 2016.[28]

The incidence of hiccups (0.8%) was found to be lower in our setting which is comparable to a study conducted by Chopra *et al.*

Table 2: Treatment-related Adverse Drug Reactions and Drugs implicated

Class (ATC Code)	Drugs	ATC code	Frequency	Percentage
Alkylating agents L01A	Cyclophosphamide	L01AA01	41	8.2
	Ifosfamide	L01AA06	8	1.6
	Bendamustine	L01AA09	4	0.8
Antimetabolites L01B	Gemcitabine	L01BC05	40	8
	Capecitabine	L01BC06	30	6
	Cytarabine	L01BC01	15	3
	Fluorouracil	L01BC02	10	2
	Methotrexate	L01BA01	6	1.2
	Decitabine	L01BC08	5	1
	Pemetrexed	L01BA04	1	0.2
	Cladribine	L01BB04	1	0.2
Plant alkaloids and Natural products L01C	Paclitaxel	L01CD01	87	17.4
	Etoposide	L01CB01	28	5.6
	Vincristine	L01CA02	26	5.2
	Docetaxel	L01CD02	22	4.4
	Vinblastine	L01CA01	5	1
Cytotoxic antibiotics and related substances L01D	Doxorubicin	L01DB01	61	12.2
	Bleomycin	L01DC01	12	2.4
	Daunorubicin	L01DB02	7	1.4
	Dactinomycin	L01DA01	2	0.4
Other anti - neoplastic agents L01X	Cisplatin	L01XA01	123	24.6
	Carboplatin	L01XA02	59	11.8
	Oxaliplatin	L01XA03	26	5.2
	Bortezomib	L01XX32	21	4.2
	Rituximab	L01XC02	15	3
	Arsenic trioxide	L01XX27	14	2.8
	Imatinib	L01XE01	5	1
	Epirubicin	L01DB03	5	1
	Nivolumab	L01XC17	3	0.6
	Irinotecan	L01XX19	3	0.6
	Trastuzumab	L01XC03	2	0.4
	Erlotinib	L01XE03	2	0.4
	Asparaginase	L01XX02	2	0.4
	Procarbazine	L01XB01	1	0.2
	Pazopanib	L01XE11	1	0.2
	Bevacizumab	L01XC07	1	0.2
Immunosuppressants L04A	Lenalidomide	L04AX04	6	1.2
	Thalidomide	L04AX02	4	0.8

2016.[29] In contrast to it, Wahlang *et al.*[19] found that there is a higher incidence of hiccups (7.5%) in their study.

Cancer chemotherapeutic drugs can alter the metabolism of an individual by changing the taste sensation, thereby leading to weight loss. Therefore, symptoms of weakness and weight loss were observed in 2.2% and 0.2% of patients respectively, which is less when compared with the study conducted by Wahlang *et al.*[19]

In our study, a total of only 4% of patients experienced alopecia/hairloss and it is significantly less when compared with 51% and 58% that was stated in some other studies.[13,30]

It was observed from our study that 1% of patients had 4-fold elevations of their liver enzymes due to administration of cytarabine, gemcitabine and arsenic trioxide. All 5 patients were hospitalized immediately and the offending drugs were withdrawn. Follow-up was done and once liver enzymes returned to normal levels or upper normal, the lower dose of the drug was reintroduced into the treatment regimen and monitored accordingly.

On scrutinizing the causal association of the ADRs with the aid of the Naranjo Scale, we observed that 91.6% of the reactions were probable, 7.2% of the reactions were possible and 1.2% of the reactions were definite. With the use of this same scale, two other studies reported 100% and 61% of probable scores for causality.[11,31]

Analysis of the severity of ADRs using the Modified Hartwig and Siegel scale showed that 80.2% of ADRs were of moderate severity, which is similar to a study conducted by Kishore *et al.* 2018.[32] 11.6% of ADRs were mild and 8.2% of ADRs were severe. Assessment of the preventability of ADRs by the

Schumock and Thornton Scale showed that 73.2% of the ADRs were not preventable. 13.2% of ADRs were definitely preventable and 13.6% of ADRs were probably preventable. In contrast to this, Sharma *et al.*[14] found that 30.8% of ADRs were definitely preventable and Wahlang *et al.*[19] found that 45.3% of ADRs were probably preventable. ADRs observed in this study like vomiting, weakness, constipation, and cough could have been prevented with meticulous premedication and proper dietary counseling before the initiation of chemotherapy.

Conclusions

Early detection of drug toxicity during treatment will help physicians to modify the doses or drug-regimen to minimize toxic effects. Exploring the pattern of ADRs associated with anti-neoplastic therapy in a tertiary care hospice gives crucial insights in relation to the causality, severity, and preventability of reported ADRs. Pharmacovigilance helps in reducing the ADRs by changing the dosage of the medication and also alleviates the economic burden of ADR management to the afflicted and society in general. Our study has endeavored to unravel the baseline profile regarding the safety of anticancer drugs in the Uttarakhand area.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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