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. 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. 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. 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
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. 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.

**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. 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, 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, 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.

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. However, few studies show that females have a higher incidence of ADRs.

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. 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. A similar study by Mrugank and Haresha, 2013 observed that gastrointestinal and breast cancers were more commonly associated with ADRs. Another study showed that patients afflicted with lung cancer and breast cancer encountered ADRs...
A recent study by Aghamohammadi et al. showed that body pain was the most common ADR. Some other studies have highlighted nausea and vomiting as the commonest ADRs. 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. 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, 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.

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. Case reports regarding bortezomib-induced peripheral neuropathy are available in the literature. 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 blockade of NF-kB activation which in turn would inhibit nerve growth factors required for neuronal survival. 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.

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.
In contrast to it, Wahlang et al. 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.

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.

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.

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. 11.6% of ADRs were mild and 8.2% of ADRs were severe. Assessment of the preventability of ADRs by the

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

| Class (ATC Code) | Drugs             | ATC code | Frequency | Percentage |
|------------------|-------------------|----------|-----------|------------|
|                | Alkylating agents |          |           |            |
|                | Cyclophosphamide  | L01AA01  | 41        | 8.2        |
| L01A            | Ifosfamide        | L01AA06  | 8         | 1.6        |
| L01B            | Bendamustine      | L01AA09  | 4         | 0.8        |
| Antimetabolites | Gemcitabine       | L01BC05  | 40        | 8          |
| L01B            | Capetitabine      | L01BC06  | 30        | 6          |
| L01B            | Cytarabine        | L01BC01  | 15        | 3          |
| L01B            | Fluorouracil      | L01BC02  | 10        | 2          |
| L01B            | Methotrexate      | L01BA01  | 6         | 1.2        |
| L01B            | Decitabine        | L01BC08  | 5         | 1          |
| L01B            | Pemetrexed        | L01BA04  | 1         | 0.2        |
| L01B            | Cladribine        | L01BB04  | 1         | 0.2        |
| Plant alkaloids and Natural products | Paclitaxel | L01CD01  | 87        | 17.4       |
| L01B            | Etoposide         | L01CB01  | 28        | 5.6        |
| L01B            | Vincristine       | L01CA02  | 26        | 5.2        |
| L01B            | Docetaxel         | L01CD02  | 22        | 4.4        |
| L01B            | Vinblastine       | L01CA01  | 5         | 1          |
| Other anti-neoplastic agents | Doxorubicin | L01DB01  | 61        | 12.2       |
| L01D            | Bleomycin         | L01DC01  | 12        | 2.4        |
| L01D            | Daunorubicin      | L01DB02  | 7         | 1.4        |
| L01D            | Dactinomycin      | L01DA01  | 2         | 0.4        |
| Cytotoxic antibiotics and related substances | | | | |
| L01D            | Gisplatin         | L01XA01  | 123       | 24.6       |
| L01X            | Carboplatin       | L01XA02  | 59        | 11.8       |
| L01X            | Oxalplatin        | L01XA03  | 26        | 5.2        |
| L01X            | Bortezomib        | L01XX32  | 21        | 4.2        |
| L01X            | Rituximab         | L01XX02  | 15        | 3          |
| L01X            | Arsenic trioxide  | L01XX27  | 14        | 2.8        |
| L01X            | Imatinib          | L01XE01  | 5         | 1          |
| L01X            | Epirubicin        | L01DB03  | 5         | 1          |
| L01X            | Nivolumab         | L01XC17  | 3         | 0.6        |
| L01X            | Irinotecan        | L01XX19  | 3         | 0.6        |
| L01X            | Trastuzumab       | L01XC03  | 2         | 0.4        |
| L01X            | Erlotinib         | L01XE03  | 2         | 0.4        |
| L01X            | Asparaginase      | L01XX02  | 2         | 0.4        |
| L01X            | Procarbazine      | L01XB01  | 1         | 0.2        |
| L01X            | Pazopanib         | L01XE11  | 1         | 0.2        |
| L01X            | Bevacizumab       | L01XC07  | 1         | 0.2        |
| L01X            | Imatinib          | L01XE01  | 5         | 1          |
| L01X            | Pazopanib         | L01XE11  | 1         | 0.2        |
| L01X            | Bevacizumab       | L01XC07  | 1         | 0.2        |
| L01X            | Nivolumab         | L01XC17  | 3         | 0.6        |
| L01X            | Erlotinib         | L01XE03  | 2         | 0.4        |
| L01X            | Pazopanib         | L01XE11  | 1         | 0.2        |
| L01X            | Bevacizumab       | L01XC07  | 1         | 0.2        |
| Immunosuppressants | Lenalidomide      | L04AX04  | 6         | 1.2        |
| L04A            | Thalidomide       | L04AX02  | 4         | 0.8        |
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. found that 30.8% of ADRs were definitely preventable and Wahlang et al. 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 patterns 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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Conflicts of interest

There are no conflicts of interest.

References

1. Stewart BW. Kleihues Pe World Cancer Report. Lyon, France: Internat. Agency Res. on Cancer Press; 2003.
2. Alison MR. Cancer. Encyclopedia of Life Sciences. Chichester, UK: John Wiley and Sons; Ltd. 2001.
3. Brunton L, Chabner B, Goodman and Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw Hill; 2011. p. 1667-75.
4. Warr DG. Chemotherapy and cancer-related nausea and vomiting. Curr Oncol 2008;15(Suppl 1):S4.
5. WHO Meeting on the Role of the Hospital in International Drug Monitoring (1968: Geneva S, Organization WH. International drug monitoring: The role of the hospital, report of a WHO meeting [held in Geneva from 18 to 23 November 1968] [Internet]. World Health Organization; 1969 [cited 2020 Feb 06]. Available from: https://apps.who.int/iris/handle/10665/40747.
6. Gandhi TK, Bartel SB, Shulman LN, Verrier D, Burdick E, Cleary A, et al. Medication safety in the ambulatory chemotherapy setting. Cancer Interdiscip Int J Am Cancer Soc 2005;104:2477-83.
7. WHO Collaborating Centre for Drug Statistics Methodology [Internet]. ATC/DDD Index; 2019. [cited 2019 Oct 23]. Available from: https://www.whocc.no/atc_ddd_index/.
8. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
9. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992;49:2229-32.
10. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm 1992;27:538.
11. Goyal YN, Solanki KC, Mistry RA, Joshi ND, Singh AP, Gajera MV. Pattern of adverse drug reactions due to cancer chemotherapy in tertiary care teaching hospital in Gujarat. Med Sci 2014;3:333-5.
12. Prasad A, Datta PP, Bhattacharya J, Pattanayak C, Chauhan AS, Panda P. Pattern of adverse drug reactions due to cancer chemotherapy in a tertiary care teaching hospital in Eastern India. J Pharmacovigil 2013;1:107.
13. Poddar S, Sultana R, Sultana R, Akbor MM, Azad MAK, Hasnat A. Pattern of adverse drug reactions due to cancer chemotherapy in tertiary care teaching hospital in Bangladesh. Dhaka Univ J Pharm Sci 2009;8:11-6.
14. Sharma A, Kumari KM, Manohar HD, Baity KL, Thomas J. Pattern of adverse drug reactions due to cancer chemotherapy in a tertiary care hospital in South India. Perspect Clin Res 2015;6:109-15.
15. Jose J, Rao PG. Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. Pharmacol Res 2006;54:226:33.
16. Mallik S, Palaian S, Ojha P, Mishra P. Pattern of adverse drug reactions due to cancer chemotherapy in a tertiary care hospital in Nepal. Pak J Pharm Sci 2007;20:214-8.
17. Gunaseelan V, Mandal SK, Prasad VN, Khumukcham R, Devi KKP, Singh TT. Adverse drug reactions to cancer chemotherapy in a regional cancer center in Northeast India. Int J Pharm Sci Res 2014;5:3358.
18. Mrugank BP, Hareesha RP. Prospective observational, non-randomized, parallel sequence study for assessment of adverse drug reactions due to chemotherapeutic treatment in different types of cancer patients. Int J Pharm Sci Res 2013;4:386.
19. Wahlang JB, Naishram PD, Brahma DK, Sarkar C, Lahon J, Nongkynrih BS. Adverse drug reactions due to cancer chemotherapy in a tertiary care teaching hospital. Ther Adv Drug Saf 2017;8:61-6.
20. Aghamohammadi H, Shrestha S, Kavousi S, Milton B. Assessment of prescribing pattern of chemotherapy drugs and monitoring of adverse drug reaction in cancer patients. Int J Pharm Sci Invent 2019;8:42-51.
21. Keshri USP, Kumari K, Mahato SK, Kumar A, Pratim P. A study of adverse drug reactions in cancer patients due to chemotherapy in a tertiary care hospital. IOSR Journal of Dental and Medical Sciences 2017;16: 89-93.
22. Lavan AH, O’Mahony D, Buckley M, O’Mahony D, Gallagher P. Adverse drug reactions in an oncological population: Prevalence, predictability, and preventability. Oncologist 2019;24:e968-77.

23. Amartya DE. Monitoring of suspected adverse drug reactions in oncology unit of an urban multispeciality teaching hospital. Int J Res Pharm Biomed Sci 2010;1:1-32.

24. Kirthi C, Afzal A, Reddy M, Ali SA, Yerramilli A, Sharma S. A study on the adverse effects of anticancer drugs in an oncology center of a tertiary care hospital. Int J Pharm Pharm Sci 2014;6:580-3.

25. Meregalli C, Canta A, Carozzi VA, Chiorazzi A, Oggioni N, Gilardini A, et al. Bortezomib-induced painful neuropathy in rats: A behavioral, neurophysiological and pathological study in rats. Eur J Pain 2010;14:343-50.

26. Mauermann ML, Blumenreich MS, Dispenzieri A, Staff NP. A case of peripheral nerve microvasculitis associated with multiple myeloma and bortezomib treatment. Muscle Nerve 2012;46:964-70.

27. Singh M, Thomas VM, Mulay S. Bortezomib-induced motor neuropathy: A case report. J Oncol Pharm Pract. 2020:1078155220904153. doi: 10.1177/1078155220904153. [Epub ahead of print]

28. Grammatico S, Cesini L, Petrucci MT. Managing treatment-related peripheral neuropathy in patients with multiple myeloma. Blood Lymphat Cancer Targets Ther 2016;6:37.

29. Chopra D, Rehan HS, Sharma V, Mishra R. Chemotherapy-induced adverse drug reactions in oncology patients: A prospective observational survey. Indian J Med Paediatr Oncol 2016;37:42-6.

30. Surendiran A, Balamurugan N, Gunaseelan K, Akhtar S, Reddy KS, Adithan C. Adverse drug reaction profile of cisplatin-based chemotherapy regimen in a tertiary care hospital in India: An evaluative study. Indian J Pharmacol 2010;42:40-3.

31. Singh S, Dhasmana DC, Bisht M, Singh PK. Pattern of adverse drug reactions to anticancer drugs: A quantitative and qualitative analysis. Indian J Med Paediatr 2017;38:140-5.

32. Kishore P, Meghana G, Reddy BP, Raghavaiah KV. Pattern of adverse drug reactions and its management in female cancer patients in a private hospital in Telangana, India. Asian J Pharm Res Dev 2018;6:45-53.