International Journal of Basic & Clinical Pharmacology
Ismail SH et al. Int J Basic Clin Pharmacol. 2024 Sep;13(5):593-598
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20242054

Original Research Article

Assessment of pattern of adverse drug reactions with chemo-therapeutic drugs in a tertiary care hospital of Government Medical College Anantnag: a prospective observational study

Sheikh Hanan Ismail, Asra Jabeen, Masrat Nabi*, Nasreen Chashoo, Sami Magray

Department of Pharmacology, GMC, Anantnag, Jammu and Kashmir, India

Received: 04 July 2024
Revised: 18 July 2024
Accepted: 19 July 2024

***Correspondence:**
Dr. Masrat Nabi,
Email: masratnabi1989@gmail.com

ABSTRACT

Background: Adverse drug reactions (ADRs) are a global problem. The high toxicity of chemo-therapeutic agents makes assessment of ADR's due to anti-cancer drugs essential. The present study is done with the aim to assess and evaluate the pattern of ADR's due to anti-cancer therapy in hospitalized patients and to analyse the causality and severity of these reactions.

Methods: A prospective observational study was conducted in department of pharmacology after getting approval from institutional ethics committee, GMC Anantnag over a period of 1 year. Patients of either sex with age >18 years was included. Data was collected directly from admitted patients in the oncology department and also from their medical case files. Causality and severity of ADRs were assessed by using the WHO-UMC causality scale and modified Hartwig and Seigel severity scale, respectively.

Results: A total of 982 ADRs were reported from 442 patients. Mean age of all patients was 37.49±11.88 years with 260 (58.82%) females and 182 (41.17%) males. Colorectal carcinoma (18.55%) was found to be the most common. Among 442 patients included in this study, 982 ADRs were recorded, with the most common being nausea/vomiting (n=166, 16.90%) followed by alopecia (n=142, 14.46%) and skin rashes (n=121, 12.32%). On causality assessment, as per WHO-UMC criteria 85.78% of the reactions were probable and 8.26% were possible. The severity of the reported reactions based on modified Hartwig and Siegel scale showed 742 (75.56%) ADRs to be mild, 227 (23.1%) ADRs to be moderate and 13 (1.32) to be severe.

Conclusions: ADRs are most important causes of morbidity and mortality and increase the economic burden on patient and society. 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. However, early detection of the ADRs may help to modify the doses or the drug regimen to minimize the adverse effects.

Keywords: Chemotherapy drugs, ADRs, Causality, Pharmacovigilance, World health organization, Uppsala monitoring centre, Modified Hartwig and Siegel scale

INTRODUCTION

Cancer has become a global concern and is the leading cause of death worldwide. According to international agency for research on cancer, GLOBOCAN 2020 (The global cancer observatory), 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] In India, the projected number of cancer patients is 1,392,179 and the incidence of cancer was about 98.7 per 100,000 population in the year 2020.[2] Cancer is treated in many different ways like radiation therapy, hormonal therapy, biological

therapy, chemotherapy, surgery, and immunotherapy.[3] But chemotherapeutic agents having narrow therapeutic index are more cytotoxic and can damage the normally dividing cells along with the cancerous cells. Patients taking anticancer drugs are more prone to develop ADRs because of multidrug treatments.[4] The prevalence of ADRs of anticancer drugs, in Indian context, is 10-12%.[5] Elderly and hospitalized patients (16.6%) are more susceptible to develop ADRs than the adult population (4.1%).[6]

As defined by world health organization (WHO), ADRs 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.[7]

According to epidemiological studies, ADRs are the fourth to sixth leading cause of death with an incidence of about 7%.[8] Impact of ADRs on patients includes deterioration of quality of life, increased hospitalisation, economic burden to health management and increased mortality rate. The estimated cost to treat ADRs is 1.7% of total budget of hospital.[9] As ADRs are inevitable, so ADR monitoring has become an important tool to detect uncommon and occasionally serious ADRs, ensuring patient safety.

Cancer treatment includes single and combination therapies of anti-cancer drugs, which is one of the common causes of ADR in a tertiary care hospital. Providing efficient health care to the public is met with various challenges and the frequent occurrence of drug toxicity is a major setback in this context. Lack of awareness among healthcare professionals, fear of litigations on the part of the prescriber, lack of time to report, insufficient hospital staff are main causes of under-reporting of ADRs.[10,11] The ADR reporting rate in India is less than 1% compared to the worldwide rate of 5%.[12] So, Pharmacovigilance is aimed at early detection of unknown adverse reactions, detection of increase in frequency of known adverse reactions, identification of risk factors and dissemination of information.[13] Most of the time ADRs remain unreported. ADRs caused due to chemotherapy is very commonly seen resulting in 6.5%-10.9% of hospital admission and mortality rates 0.15%-2.9%.[14]

So, hospital-based ADR monitoring and reporting programs can help in identifying and assessing the risks associated with the use of drugs. This data may help the prescribers to identify ADRs and deal with them more efficiently, and also help in preventing the occurrences of these ADRs in future.[15] ADR monitoring and reporting activity is still in the early stages in India. Lack of an organized and efficient ADR monitoring and reporting program is posing a great challenge to drug safety screening in the Indian subcontinent.[16] Hence, it is necessary to recognize the pattern of ADRs related to anticancer drugs to improve the quality of life and also to reduce cost of ADR related hospitalization among cancer patients. Thus, the present study aimed to determine the nature and severity of ADRs in cancer patients.

The present study was done in a tertiary care hospital, with the objective to assess the pattern of ADRs from various anti-cancer drugs. Assessment of causality and severity of ADRs was also done to know the pattern of ADRs and make an effort to manage them accordingly.

Aim

Aim of the study was to assess and evaluate the pattern of ADRs due to anti-cancer therapy in hospitalized patients and to analyze the causality and severity of these reactions.

METHODS

Study design

This study was a prospective and observational study done for a period of one year from July 2023 to June 2024. The study was started after getting approval from the ethics committee. The study was conducted in the department of pharmacology and the department of oncology of govt. medical collage Anantnag.

Inclusion criteria

Patients with age group >18 years, patients of either sex, all cancer patients admitted to the oncology department during study period, on at least 1 anti-cancer drug and patients with at least 1 ADR reported were included in study.

Exclusion criteria

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

Patients who developed ADR due to fresh blood or blood products infusion, or due to intentional or accidental poisoning and those with a history of drug abuse and intoxication were excluded.

Sample size

Cancer patients admitted to the oncology ward during the study period, only those who fulfilled the inclusion criteria were enrolled in the study. ADRs were observed in 442 patients were studied for the present study, who had gone through 982 ADRs which are assessed in our study.

Study tools

ADRs reported to ADR monitoring centre (AMC) of department of pharmacology were used for collection of data. The protocol is based on the guidelines provided by standard operating procedure of Indian pharmacopoeia commission (IPC/PvPV/QA/013). ADRs are updated manually in Vigiflow software provided by Uppsala monitoring centre, WHO collaborating centre, Uppsala

Sweden.[17] ADRs are noted during patient follow-up either by patient's own complain or by leading questions asked by physicians. After receiving the ADR's, the treating physicians were contacted by our department centre for further collection of data and all follow up details. The ADRs were categorized based on WHO-UMC criteria for causality assessment. The WHO causality assessment scale determines the causal relationship of a suspected drug to the ADR in question and causality is categorized into "certain," "probable," "possible," "unlikely, and severity of ADR assessed by modified Hartwig and Siegel scale classifies as mild, moderate, and severe with various levels, depending on a number of factors like the requirement for change in treatment, duration of hospital stay and the disability produced by the ADR.[8] 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.

Statistical analysis

Descriptive statistics such as percentage, mean, and standard deviations were used to describe the study variables. 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 present study was a prospective, randomized, observational study undertaken to evaluate the pattern of ADRs due to anti-cancer therapy in hospitalized patients and to analyze the causality and severity of these reactions. The baseline characteristics of the patients are shown in Table 1. A total of 442 patients with 260 (58.82%) females and 182 (41.17%) males were included in the study. And ADRs which were reported from the patients were updated on VigiFlow and were analyzed. Mean age of all patients was 37.49±11.88 years. Majority of the patients were married (63.80%). Most of them (72.62%) had never smoked, while some (27.37%) were current smokers (Table 1).

Table 1: Demographic details of patients, (n=442).

Patient characteristics		N (%)
Age (in years)	Mean±SD	37.49±11.88
Sex	Male	182 (41.17)
	Female	260 (58.82)
Marital status	Married	282 (63.80)
	Unmarried	202 (45.70)
Smoking	Smoker	121 (27.37)
	Non-smoker	321 (72.62)

In our study colorectal carcinoma (18.55%) was found to be the most common cancer followed by gastric carcinoma (13.80%), ovarian carcinoma (11.99%) and breast carcinoma (10.40%) (Table 2).

Table 2: Distribution of cancers in study population, (n=442).

Types of cancers	N (%)
Colorectal carcinoma	82 (18.55)
Gastric carcinoma	61 (13.80)
Ovarian carcinoma	53 (11.99)
Breast carcinoma	46 (10.40)
Esophagus carcinoma	37 (8.37)
Prostatic carcinoma	32 (7.2)
Leukemia's	23 (5.20)
Multiple myeloma	18 (4.07)
Non-Hodgkin's lymphoma	16 (3.61)
Cervical carcinoma	12 (2.71)
Endometrial carcinoma	7 (1.58)
Lung carcinoma	7 (1.58)
Bladder carcinoma	9 (2.03)
Testicular carcinoma	5 (1.13)
Hodgkin's lymphoma	3 (0.67)
Others (liver, retina, penile, rectum, skin)	31 (7.01)

Among 442 patients included in this study, 982 ADRs were recorded, with the most common being nausea/ vomiting (n=166, 16.90%), followed by alopecia (n=142, 14.46%) and skin rashes (n=121, 12.32%) (Table 3).

Table 3: Pattern of ADR in study population, (n=982).

ADRs	N (%)
Nausea/ vomiting	166 (16.90)
Alopecia	142 (14.46)
Skin rashes	121 (12.32)
Anorexia	96 (9.77)
Diarrhea	80 (8.14)
Fatigue	64 (6.51)
Anemia	51 (5.1)
Fever	43 (4.3)
Weight changes	39 (3.97)
Abdominal pain	21 (2.13)
Dizziness	19 (1.9)
Myalgia	16 (1.6)
Itching	14 (1.42)
Leucopenia	14 (1.42)
Constipation	12 (1.22)
Insomnia	10 (1.01)
Neuropathy	10 (1.01)
Burning micturition	9 (0.91)
Buccal mucus eruptions	8 (0.81)
Thrombocytopenia	6 (0.61)
Hepatoxicity	5 (0.50)
Head ache	5 (0.50)
Hand and foot syndrome	4 (0.40)
Melanonychia	3 (0.30)
pancytopenia	3 (0.30)
Others (xerostomia, urticaria, urinary tract infections, pulmonary fibrosis, bitter taste and cough)	21 (2.13)

Assessment of causality by WHO causality assessment scale indicated that 85.78% of the reactions were probable and 8.26% were possible. Only 4.33% of ADRs were categorized as certain as much rechallenge was not attempted in most of the patients (Table 4).

The severity of the reported reactions based on modified Hartwig and Siegel scale showed 742 (75.56%) ADRs to be mild, 227 (23.1%) ADRs to be moderate and 13 (1.32) ADRs to be severe (Table 5).

Table 4: WHO-UMC causality assessment scale, (n=982).

Severity	N (%)
Mild	742 (75.56)
Moderate	227 (23.11)
Severe	13 (1.32)

Table 5: Hartwig and Siegel severity assessment scale, (n=982).

Severity	N (%)
Mild	742 (75.56)
Moderate	227 (23.11)
Severe	13 (1.32)

DISCUSSION

The ADRs developed because of the use of anticancer drugs in a tertiary care hospital of GMC Anantnag which were collected, analyzed and reported. Therefore, documentation and reporting of ADRs becomes a crucial element in clarifying the side effect profile of a drug. This may help to prevent future occurrences of incidents. A noble, ethical medical practice needs accurate and unbiased information about drugs. This is possible only by a vigorous drug safety monitoring program.[2] An efficiently operating hospital-based reporting program may be helpful in providing an insight into the potential problems of drug usage in an institution. In our study, we evaluated the pattern of ADRs in anticancer drugs were observed more in female patients (58.82%) than in male patients. This finding was found to be comparable with other studies.[18,19] On the contrary some studies showed male preponderance more than females.[20,21] Hormonal changes in different stages of life causing an alteration in the pharmacokinetic profile of the drugs can attribute to the increased incidence in female patients.[21] Majority of the patients (82.6%) were nonsmokers. Similar results were reported by Poddar et al.[1] Most common cancer in this study was found to be Colorectal carcinoma (18.55%) which has similarity to the study done in eastern India by Prasad et al.[22] In this study the most common ADR observed was nausea and vomiting (14.46%) and alopecia (12.32%).

Other ADRs found were anorexia (16.90%), skin rashes (12.32%) anemia, diarrhea leucopenia, neuropathy, etc. The study finding was in contrast to studies carried out by Sharma et al and Sunny et al where the most common ADRs were observed to be infections and nausea and vomiting, respectively.[18,23] Chemotherapy-induced nausea and vomiting is due to the activation of chemoreceptor trigger zone.[22]

The causality assessment was done according to WHO-UMC causality assessment system which categorized ADRs as 85.78% 'probable' and ADRs as 'possible' 8.26%. Similarities have been observed in some other studies.[24,25] On the contrary to this study, most of the ADRs are categorized as 'possible' in the study done by Chopra et al.[26] Severity of the reactions was assessed using modified Hartwig and Siegel scale which showed most of the ADRs as mild (75.56%) followed by moderate ADRs (23.11%) and (1.32%) severe ADRs. This finding of this study correlates with the study done by Wahlang et al.[20] But the study findings are in contrast to some other studies.[18,27] The present study has been conducted at a tertiary care hospital in GMC Anantnag and the findings under different categories that have been analyzed were almost similar to that found in other parts of the country but in order to generalize this as a finding of the Northeast region, authors need a larger scale study with more numbers of healthcare centres involving other states of the region.

This study provides basic information regarding the safety profile of various anticancer drugs in a variety of cancers. We have also assessed four different parameters of the ADR noted, namely the causality, severity, predictability, and preventability. To the best of our knowledge, this is the first study of its kind from GMC Anantnag.

Limitations

A major limitation of the study was incomplete documentation of data regarding ADRs in the case reports and also incomplete laboratory investigations. Non reporting of ADRs may also have affected the observed pattern of results.

CONCLUSION

Anticancer drugs have high potential to damage the rapidly dividing cells in the body and thereby can cause ADRs. Hence, regular and sustained monitoring with proper care and early reporting can minimize the occurrence of ADRs, increase patient compliance, reduce morbidity and mortality and also reduce economic burden to the patients and the society. Awareness should be created among all healthcare professionals to encourage them for spontaneous reporting. Therefore, a comprehensive and effective pharmacovigilance is the need of the hour to reduce the burden of ADRs and thereby improve the benefit harm ratio of the drugs.

ACKNOWLEDGEMENTS

Authors would like to thank head of department, all faculties and staff of radiation oncology, department of

GMC Anantnag. Authors are also grateful to pharmacovigilance program of India and Indian pharmacopoeia commission.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee GMC ANANTNAG (Approval Number:IEC/GMCA/23/072)

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, et al. Cancer statistics for the year 2020: An overview. Int J Cancer. 2021;149(4):778-89.
2. Mathur P, Kumar SK, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, et al. Cancer statistics, 2020: Report from National Cancer Registry Programme, India. JCO Glob Oncol. 2020;6:1063-75.
3. Wellstein A. General principles in the pharmacotherapy of cancer. In: Brunton LL, Hilal-Dandan R, Knollmann BC, editors. Goodman and Gilman's the pharmacological basis of therapeutics, 13th ed, McGraw Hill Education, New York. 2018;1161-6.
4. Kirthi C, Afzal A, Reddy M, Ali 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(2):18-21.
5. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18820 patients. BMJ. 2004;329(7456):15-9.
6. Jose J, Rao PG. Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. Pharmacol Res. 2006;54(3):226-33.
7. World Health Organization. The use of the WHO-UMC system for standardized case causality assessment. 2011. Available at: https://www.who.int/docs/default-source/medicines/pharmacovigilance/whocausality-assessment.pdf. Accessed on 3 June 2024.
8. Brown SD, Jr, Landry FJ. Recognising, reporting, and reducing adverse drug reactions. South Med J. 2001;94(4):370-3.
9. Couffignal AL, Lapeyre-Mestre M, Bonhomme C, Bugat R, Montastruc JL. Adverse effects of anticancer drugs: Apropos of a pharmacovigilance study at a specialized oncology institution. Therapie. 2000;55(5):635-41.
10. Adithan C. National pharmacovigilance programme. Indian J Pharmacol. 2005;37(6):347.
11. Sharma A, Kumari KM, Manohar HD, Bairy 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(2):109-15.
12. Upadhyaya HB, Vora MB, Nagar JG, Patel PB. Knowledge, attitude and practices toward pharmacovigilance and adverse drug reactions in postgraduate students of tertiary care hospital in Gujarat. J Adv Pharm Technol Res. 2015;6(1):29-34.
13. World Health Organisation. Safety monitoring of medicinal products. Guidelines for setting up and running a pharmacovigilance centre. Available at: http://www.who-umc.org/graphics/4807. Accessed on 1 June 2024.
14. Krishnarajan D, Sivasakthi K, Ariyamol R, Kumar DN, Varghese S. A prospective observational study of chemotherapy induced adverse drug reaction and the quality of life in cancer patients in a tertiary care hospital. J Cancer Res Therapeutics. 2021;17(2):530.
15. Arulmani R, Rajendran SD, Suresh B. Adverse drug reaction monitoring in a secondary care hospital in South India. Br J Clin Pharmacol. 2008;65:210-6.
16. Sriram S, Ghasemi A, Ramasamy R, Devi M, Balasubramanian R, Ravi TK, et al. Prevalence of adverse drug reactions at a private tertiary care hospital in south India. J Res Med Sci 2011;16(1):16-25.
17. UMC. About VigiFlow-Uppsala Monitoring Centre. Available at: https://www.who-umc.org›global-pharmacovigilance. Accessed on 1 June 2024.
18. Sharma A, Kumari KM, Manohar HD, Bairy 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(2):109-15.
19. 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(1):40-3.
20. Wahlang JB, Laishram 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(2):61-6.
21. Soldin OP, Chung SH, Mattison DR. Sex differences in drug disposition. J Biomed Biotechnol. 2011;2011:187103.
22. Prasad A, Datta PP, Bhattacharya J, Pattanayak C, Chauhan AS, Panda P, et al. Pattern of adverse drug reactions due to cancer chemotherapy in a tertiary care teaching hospital in Eastern India. J Pharmacovigilance. 2013;1(2):107.
23. Sunny S, Thampi A, Kennedy J, Shetty N, Babasahib SK, Chacko C. Assessment of adverse effects of most commonly prescribed anticancer drugs in a tertiary care teaching hospital. Indian J Pharmacy Pract. 2017;10(4):270-5.
24. Saini VK, Sewal RK, Ahmad Y, Medhi B. Prospective observational study of adverse drug reactions of anticancer drugs used in cancer treatment in a tertiary care hospital. Indian J Pharm Sci. 2015;77(6):687-93.
25. Rout A, Panda RK, Mishra V, Parida P, Mohanty S. Pharmacovigilance in cancer chemotherapy in regional cancer center of Eastern India: Prospective observational study. Int J Basic Clin Pharmacol. 2017;6(8):1910-6.

26. Chopra D, Rehan HS, Sharma V, Mishra R. Chemotherapy-induced adverse drug reactions in oncology patients: A prospective observational survey. Indian J Med Paediatric Oncol. 2016;37(1):42-6.
27. Swathi B, Bhavika D, Begum N. Adverse drug reaction profiles of commonly used platinum compounds in cancer chemotherapy. Int J Basic Clin Pharmacol. 2015;4(2):284-9.

Cite this article as: Ismail SH, Jabeen A, Nabi M, Chashoo N, Magray S. Assessment of pattern of adverse drug reactions with chemo-therapeutic drugs in a tertiary care hospital of Government Medical College Anantnag: a prospective observational study. Int J Basic Clin Pharmacol 2024;13:593-8.