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Original Article

Pharmacology Section

A Retrospective Study on Adverse Drug Reactions of Anticancer Drugs in a Tertiary Care Hospital in Northeast India

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ABSTRACT

Introduction: Anticancer drugs account to high susceptibility towards Adverse Drug Reactions (ADRs) due to their narrow therapeutic window and increased toxicity, which makes pharmacovigilance studies essential.

Aim: To determine the nature and severity of ADRs in cancer patients based on the reports received from the Department of Radiation Oncology to the Pharmacovigilance centre of a tertiary care hospital.

Materials and Methods: A retrospective, descriptive study was conducted in the Regional Institute of Medical Sciences (RIMS), Imphal, Manipur, India on the patients who developed ADRs due to anticancer drugs during the period from January 2018 to December 2020. These ADRs were assessed for causality using World Health Organisation- Uppsala Monitoring Centre (WHO-UMC) criteria. The data was analysed using Statistical Package for the Social Sciences (SPSS) version 21.0 and frequencies and percentages were determined for each variable.

Results: A total of 913 ADRs were reported from 334 patients. Total 62.57% females developed ADRs and age group of 51-60 years (31.14%) were affected the most. Bronchogenic carcinoma (20.9%) was found to be the most common cancer and haematological system (31.11%) was mostly affected. Most common ADRs observed were alopecia (16.32%) followed by anorexia and anaemia. Carboplatin (23.21%) followed by Cisplatin, Paclitaxel, Docetaxel were the most common drugs causing different ADRs. On causality assessment, as per WHO-UMC criteria 67.25% ADRs were 'probable' and 32.75% were 'possible'. Severity assessment using modified Hartwig and Siegel scale showed 56.41% ADRs as mild, 41.95% moderate and 1.64% severe reaction. Preventability assessment using Schumock-Thornton scale showed 44.69% ADRs were 'not preventable' whereas 41.62% ADRs were 'definitely preventable' and 13.69% were 'probably preventable'.

Conclusion: The use of anticancer drugs is associated with various adverse effects. However, early detection of the ADRs may help to modify the doses or the drug regimen to minimise the adverse effects.

Keywords: Modified hartwig and siegel scale, Pharmacovigilance, Schumock-thornton scale, World Health Organisation- Uppsala Monitoring Centre criteria

INTRODUCTION

According to International Agency for Research on Cancer, Global Cancer Observatory (GLOBOCAN) 2020, approximately 19.2 million new cancer cases and 9.9 million cancer deaths have been reported in 2020 [1]. In India, the projected number of cancer patients are 1,392,179 and the incidence of cancer is about 98.7 per 100,000 population in the year 2020 [2]. Multimodal approaches like chemotherapy, radiotherapy, immunotherapy, hormonal therapy, surgery, biological agents, cryosurgery are available for the treatment of cancer [3]. But, antineoplastic 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 hospitalised patients (16.6%) are more susceptible to develop ADRs than the adult population (4.1%) [6].

According to epidemiological studies, ADRs are the fourth to sixth leading cause of death with an incidence of about 7% [7]. 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 [8]. As ADRs are inevitable, so ADR monitoring has become an important tool to detect uncommon and occasionally serious ADRs, ensuring patient safety. Although the recent advancement of anticancer agents has increased survival rates, cancer and the treatment can debilitate the patient both physically and psychologically. The most common ADRs associated with anticancer treatment are alopecia, bone marrow suppression, nausea and vomiting, infection, pain etc. In addition to the adverse effects, some patients also develop depression, anxiety, sexual dysfunction leading to poor quality of life. The common drugs causing ADRs are taxanes, platinum compounds, alkylating agents, anticancer antibiotics etc., [9-11].

Lack of awareness among healthcare professionals, fear of litigations on the part of the prescriber, lack of time to report, insufficient hospital staffs are main causes of under-reporting of ADRs [10]. 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].

Hence, it is necessary to recognise the pattern of ADRs related to anticancer drugs to improve the quality of life and also to reduce cost of ADR related hospitalisation among cancer patients. Thus, the present study aimed to determine the nature and severity of ADRs in cancer patients.

MATERIALS AND METHODS

A retrospective, descriptive study was conducted in the Department of Pharmacology, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur, India. During the study, the Declaration of Helsinki ethical principles for medical research was followed and patients' anonymity was maintained.

As an institutional protocol, ADRs are reported to ADR Monitoring Centre (AMC) which is coordinated by the Institute's Department of Pharmacology. 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 [14]. ADRs are noted during patient follow-up either by patient's own complain or by leading questions asked by physicians. The treating physicians are then contacted by pharmacovigilance centre for collection of data. The ADRs are categorised based on WHO-UMC criteria for causality assessment.

Inclusion and Exclusion criteria: All the adverse drug event reported due to anticancer drugs from Radiation Oncology Department by both spontaneous reporting and by active surveillance, which were submitted to the AMC at the Department of Pharmacology, RIMS, Imphal under the Pharmacovigilance Programme of India from January 2018 to December 2020, were included in the study. Under-reported ADRs and patients with other co-morbidities were excluded from the study.

A total of 334 cancer patients of both sexes and all ages who developed atleast one ADR during or after the treatment with anticancer drugs were included. ADR reporting form designed by Centre for Drug Standard Control Organisation (CDSCO) was used to collect the data regarding ADRs. The demographic details (age, sex), diagnosis, suspected drugs causing ADRs, treatment details, description of the event, onset and ablation of adverse event, type of ADRs, system affected by the ADRs, outcome of the ADRs, relevant laboratory investigations were recorded.

The WHO-UMC causality assessment system was used to evaluate the causality of the ADRs. It was categorised them into certain, probable/likely, possible, unlikely, conditional/unclassified and unassessable/unclassifiable [15]. The severity of the ADRs was assessed by using modified Hartwig SC and Siegel J scale which categorises the ADRs into mild, moderate and severe reaction [16]. Preventability assessment was done according to Schumock-Thornton scale which divided ADRs into 'not preventable', 'definitely preventable' and 'probably preventable' [17].

STATISTICAL ANALYSIS

The data collected were analysed using SPSS, IBM Corporation, version 21.0 and frequencies and percentages were determined for each variable.

RESULTS

Among the 334 patients included in the study, 209 (62.57%) were females and 125 (37.43%) were males. The majority of the patients were in the age group of 51-60 years (n=104, 31.14%) [Table/Fig-1].

Patient characteristics	Number (%)
Sex	
Male	125 (37.43)
Female	209 (62.57)
Age (years)	
1-10	8 (2.39)
11-20	5 (1.50)
21-30	12 (3.59)
31-40	32 (9.58)
41-50	72 (21.56)
51-60	104 (31.14)
61-70	72 (21.56)
71-80	22 (6.59)
81-90	7 (2.09)

[Table/Fig-1]: Sex and age wise ADR distribution.

Bronchogenic carcinoma {70 (20.9%)} was found to be the most common cancer in the study group which was followed by ovarian carcinoma {32 (9.6%)} [Table/Fig-2].

Organs involved	Number (%)
Lung	70 (20.9)
Ovary	32 (9.6)
Breast	31 (9.3)
Nasopharynx	31 (9.3)
Lymphoid tissue	21 (6.2)
Cervix	19 (5.7)
Colon	19 (5.7)
Rectum	17 (5.1)
Gall bladder	14 (4.2)
Oral cavity	14 (4.2)
Oesophagus	13 (3.9)
Stomach	8 (2.4)
Uterus	6 (1.8)
Pancreas	5 (1.5)
Caecum	3 (0.9)
Pyriform sinus	3 (0.9)
Larynx	3 (0.9)
Soft tissue	3 (0.9)
Others	22 (6.6)

[Table/Fig-2]: Distribution of cancers in the study population.
*Other organs involved were retina, blood, urinary bladder, maxilla, medulla, para nasal sinus, vulva, tonsil, neuron

A total of 913 ADRs were identified and recorded. Most common ADR was alopecia {149 (16.32%)} followed by anorexia {143 (15.66%)}, anaemia {130 (14.24%)}. Other ADRs reported were leucopenia, nausea and vomiting, oral candidiasis, neuropathy itching, diarrhoea, pain abdomen, thrombocytopenia, anaphylaxis, rashes, headache, myalgia, hand and foot syndrome etc., [Table/Fig-3].

Adverse drug reactions	N (%)
Alopecia	149 (16.32)
Anorexia	143 (15.66)
Anaemia	130 (14.24)
Leucopenia	98 (10.73)
Nausea and vomiting	98 (10.73)
Oral candidiasis	40 (4.38)
Neuropathy	39 (4.27)
Bicytopenia	39 (4.27)
Itching	38 (4.16)
Diarrhoea	22 (2.40)
Pain abdomen	15 (1.64)
Thrombocytopenia	13 (1.42)
Anaphylaxis	10 (1.09)
Rashes	10 (1.09)
Headache	9 (0.98)
Myalgia	9 (0.98)
Hand and foot syndrome	8 (0.87)
Dizziness	8 (0.87)
Insomnia	6 (0.66)
Constipation	6 (0.66)
Hepatotoxicity	5 (0.55)
Facial flushing	5 (0.55)
Mucositis	5 (0.55)
Fever	5 (0.55)

Pancytopenia	4 (0.44)
Gastritis	4 (0.44)
Others	12 (1.31)

[Table/Fig-3]: Pattern of Adverse Drug Reactions (ADR) in the study population.
*Other ADRs seen were acute kidney injury, cardiotoxicity, throat pain, urinary tract infection, skin, discoloration, bitter taste, chest pain, dry cough, urine discoloration

Haematological system {284 (31.11%)} was mostly affected which was followed by gastrointestinal system {283 (31%)} and dermatological system {255 (27.93%)} [Table/Fig-4].

Systems involved	Number (%)
Haematological	284 (31.11)
Gastrointestinal	283 (31)
Dermatological	255 (27.93)
Neurological	62 (6.79)
Musculoskeletal	9 (0.98)
Nephrological	4 (0.44)
Cardiological	2 (0.22)
Others	14 (1.53)

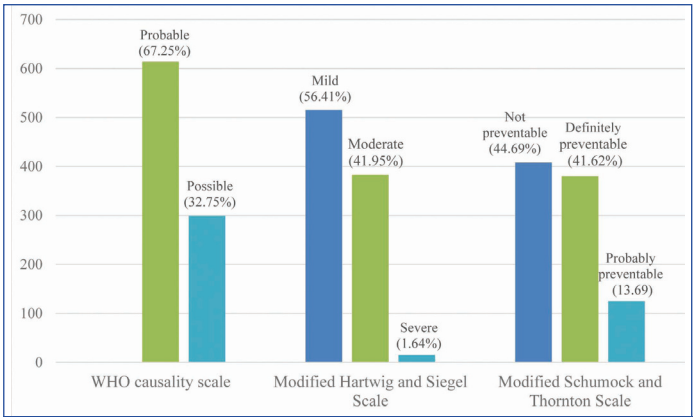
[Table/Fig-4]: Organ system wise distribution of Adverse Drug Reaction (ADR).
*Other systems involved were respiratory system, immune system, gustatory system

In this study, a total of 504 anticancer drugs were used in 334 patients. The most common suspected anticancer drug causing ADRs was Carboplatin {117 (23.21%)} followed by Cisplatin {59 (11.71%)}. Few reactions were observed with Paclitaxel, Docetaxel, Oxaliplatin, Gemcitabine, Cyclophosphamide, 5-flurouracil, Vincristine, Doxorubicin, Etoposide etc., [Table/Fig-5].

Drugs used	Number (%)
Carboplatin	117 (23.21)
Cisplatin	59 (11.71)
Paclitaxel	52 (10.32)
Docetaxel	45 (8.93)
Oxaliplatin	37 (7.34)
Gemcitabine	30 (5.95)
Cyclophosphamide	24 (4.77)
5-Fluorouracil	16 (3.17)
Vincristine	14 (2.78)
Doxorubicin	13 (2.58)
Etoposide	13 (2.58)
Capecitabine	12 (2.38)
Pemetrexed	9 (1.78)
Erlotinib	9 (1.78)
Leucovorin	8 (1.59)
Rituximab	8 (1.59)
Methotrexate	7 (1.39)
Others	31 (6.15)

[Table/Fig-5]: Drug wise Adverse Drug Reaction (ADR) distribution (n=504).
*Other drugs were Epirubicin, Irinotecan, Dactinomycin, Transtuzumab, Gefitinib, Bortezumab, Adriamycin, Ifosphamide, Decarbazine, Bevacizumab, Abiterone, Vinorelbine, Vinblastine, Imatinib, Bleomycin

Causality assessment using WHO-UMC causality assessment system showed that 614 ADRs (67.25%) were 'probable' and 299 ADRs (32.75%) were 'possible'. The severity of the reported reactions based on modified Hartwig and Siegel scale showed 515 (56.41%) ADRs to be mild, 383 (41.95%) ADRs to be moderate and 15 (1.64%) ADRs to be severe. Preventability assessment of ADRs was analysed using Schumock-Thornton preventability assessment scale which showed 408 (44.69%) ADRs were 'not preventable' whereas 380 (41.62%) ADRs were 'definitely preventable' and 125 (13.69%) ADRs were 'probably preventable' [Table/Fig-6].



[Table/Fig-6]: Causality, severity, and preventability assessment.

DISCUSSION

The ADRs developed because of the use of anticancer drugs over a period of three years in a tertiary care hospital of Northeast India were collected, analysed and reported. In the present study, ADRs due to anticancer drugs were observed in female patients (62.57%) more than in male patients. This finding was found to be comparable with other studies [10,18]. On the contrary some studies showed male preponderance more than females [19,20]. 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]. Increased incidence of cancer in females in Manipur may also contribute to this [22].

Most of the ADRs were seen in patients in the age group of 51-60 years (31.14%) which was similar to the study by Sharma A et al., in Southern India [10]. The metabolising capacity and the excretory functions in elderly patients are reduced which leads to the accumulation of drugs in the body causing increased risk of ADRs [23]. Most common cancer in this study was found to be bronchogenic carcinoma (20.9%) which has similarity to the study done in eastern India by Prasad A et al., [19].

In this study the most common ADR observed was alopecia (16.32%). This finding corresponds with the studies done by Sharma PK et al., and Saini VK et al., [11,24]. Anticancer drugs affect the highly proliferating hair follicle cells thus causing alopecia. Other ADRs found were anorexia, anaemia, leucopenia, nausea and vomiting, neuropathy, diarrhoea etc. The study finding was in contrast to studies carried out by Sharma A et al., and Sunny S et al., where the most common ADRs were observed to be infections and nausea and vomiting, respectively [10,25]. Chemotherapy-induced nausea and vomiting is due to the activation of chemoreceptor trigger zone [19]. In this study, the most common system affected due to anticancer drugs was haematological system (31.11%) followed by gastrointestinal system (31%). The ADRs observed in haematological system were anaemia, leucopenia, bicytopenia, thrombocytopenia and pancytopenia. The findings observed were to be consistent with the study done by Rout A et al., [26]. While destroying the cancer cells, anticancer drugs also damage rapidly dividing cells of bone marrow resulting in myelosuppression thus affecting red blood cells, white blood cells and platelets [19].

This study showed that the most common anticancer drug causing ADRs was Carboplatin (23.21%) followed by Cisplatin (11.71%) which was similar to other studies where ADRs were most commonly associated with the platinum compounds [10,19,27,28]. However, in contrast to this study, Poddar S and Sultana R studied that antimetabolites and alkylating agents were the most common drugs causing ADRs [29].

The causality assessment was done according to WHO-UMC causality assessment system which categorised 67.25% ADRs as 'probable' and 32.75% ADRs as 'possible'. Similarities have been observed in some other studies [24,26]. On the contrary to

Author	Region	Commonly affected age group (years)	Most common gender affected	N (%)	No. of ADRs	Common system involved	Most common ADR	Causality assessment	Severity assessment	Preventability assessment
Sharma A et al., [10]	South India	51-60	F	195	500		Infections	Probable: 65% Possible: 35%	Mild: 30.6% Moderate: 63.4% Severe: 6%	Preventable: 95.8% Not preventable: 4.2%
Sharma PK et al., [11]	Jodhpur	19-65	F	164	191	Dermatological system	Alopecia	Probable: 28.7% Possible: 70.1% Definite: 1.04%	Mild: 54.45% Moderate: 44.5% Severe: 1.05%	Preventable: 91.1% Not preventable: 8.9%
Prasad A et al., [19]	Eastern India	50-59	M	45		Haematological system	Nausea and vomiting	Probable: 62% Possible: 31% Definite: 7%		
Wahlang JB et al., [20]	Northeast India		M	70	106	Gastrointestinal system	Vomiting	Probable: 13.2% Possible: 86.7%	Mild: 77.4% Moderate: 18.9% Severe: 3.8%	Preventable: 45.3% Not preventable: 54.7%
Saini VK et al., [24]	Chandigarh		F	152		Dermatological system	Alopecia	Probable: 64.67% Possible: 35.33%		
Sunny S et al., [25]	Mangalore		F	109	450	Gastrointestinal system	Vomiting	Probable: 45.78% Possible: 40.44% Definite: 0.89%	Mild: 54.13% Moderate: 44.95% Severe: 0.92%	Definitely preventable: 46.22% Probably preventable: 20.67% Not preventable: 33.11%
Rout A et al., [26]	Odisha	41-50	F	104	329	Haematological system	Nausea and vomiting	Probable: 68.38% Possible: 31.62%	Mild: 20.36% Moderate: 69.31% Severe: 10.33%	Definitely preventable: 21.88% Probably preventable: 13.67% Not preventable: 64.45%
Chopra D et al., [27]	New Delhi	41-50	F	591		Gastrointestinal system	Nausea and vomiting	Probable: 20% Possible: 80%	Mild: 86.97% Moderate: 12.8% Severe: 0.17%	Definitely preventable: 7% Probably preventable: 42% Not preventable: 51%
Kaur K et al., [28]	Punjab	44-51	F	671	2500	Dermatological system	Alopecia			
Swathi B et al., [30]	Hyderabad	41-50	F	78	96	Gastrointestinal system	Vomiting	Probable: 35.4% Possible: 64.6%	Mild: 12.5% Moderate: 68.75% Severe: 18.75%	Definitely preventable: 47.9% Probably preventable: 15.6% Not preventable: 36.5%

[Table/Fig-7]: An overview of few studies on ADRs of anticancer drugs done in India [10,11,19,20,24-30].
F: Female; M: Male

this study, most of the ADRs are categorised as 'possible' in the study done by Chopra D et al., [27]. Severity of the reactions was assessed using modified Hartwig and Siegel scale which showed most of the ADRs as mild (56.41%) followed by moderate ADRs (41.95%) and 1.64% severe ADRs. This finding of this study correlates with the study done by Wahlang JB et al., [20]. But the study findings are in contrast to some other studies [10,30]. Preventability assessment done by Schumock-Thornton scale showed most of the ADRs were 'not preventable' which was in concordance with findings of Rout A et al., [26]. This study findings were in contrary with some other studies which showed most of the ADRs were 'definitely preventable' [25,30]. [Table/Fig-7] shows few studies comparing demographic and other parameters [10,11,19,20,24-30].

When present study findings were compared with that of the other studies carried out in other parts of the country, the most commonly affected gender, age and system are almost the same [10,18,26]. The common manifestation (alopecia) was also similar to that found in three other studies [11,24,28]. The casualty assessment showed most of the ADRs were 'probable' which was similar to that of four other studies [10,19,24,26]. The ADRs commonly encountered were of mild type [11,20,25,27] and most of them were of the 'not preventable' type which was also seen in some of the previous studies [20,26,27]. The present study has been conducted at a tertiary care hospital in Manipur and the findings under different categories that have been analysed were almost similar to that found in other parts of the country but in order to generalise 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.

Limitation(s)

The major limitation of the study was that it was a retrospective study and included only the spontaneously reported ADRs. Also failing to trace the patients and the reporting personnel for documenting incompletely described ADRs, incomplete laboratory investigations are the drawbacks of the study. Non reporting of ADRs may also have affected the observed pattern of results.

CONCLUSION(S)

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 minimise the occurrence of ADRs, increase patient compliance, reduce morbidity and mortality and also reduce economic burden to the patients and 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.

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