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ASSESSMENT OF CAUSALITY, SEVERITY AND PREVENTABILITY OF ADVERSE DRUG REACTIONS OF CANCER CHEMOTHERAPY IN A TERTIARY CARE TEACHING HOSPITAL, GUJARAT, INDIA

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Keywords:

Adverse drug reactions (ADRs), Cancer chemotherapy, Causality, Severity, Preventability, Pharmacovigilance

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ABSTRACT: Background: To evaluate the various adverse drug reactions with different cancer chemotherapy regimens, severity, causality assessment and preventability. **Methods:** This cross-sectional, observational study was carried out in the oncology department at a tertiary care teaching hospital over a period of one year. Data on Adverse Drug Reactions (ADRs) of anticancer drugs were collected of cancer patients diagnosed by a concerned clinician from the oncology department. These ADRs were assessed for causality using Naranjo's probability scale. The severity and preventability of the reported reactions were assessed using the modified Hartwig and Siegel scale and modified Schumock and Thornton scale, respectively. Data were analyzed using Descriptive Statistics and Microsoft Excel. **Results:** Out of 683 ADRs recorded from 198 patients, m/c ADRs were alopecia (21.08%), n/v (17.27%) & nail pigmentation (11.56%), *etc*. Taxanes, Platinum compounds, Nitrogen mustards, Antibiotics, and Antimetabolites were the most common group of drugs causing ADRs. On Causality Assessment showed highest ADRs were "possible" (49.34%), "probable" (47.58%) & few were "doubtful" (3.07%). Severity Assessment showed a majority of the ADRs belonged to "mild" grade (91.21%), then "moderate" (8.05%) & "severe" (0.73%). It was observed that most of the ADRs were "Not Preventable" (57.83%), "Probably Preventable" (24.3%) & lastly "Definitely Preventable" (17.86%). **Conclusions:** The study shows that most of ADRs due to anticancer drugs belonged to "possible" grade as per Causality assessment, "mild" as per Severity Assessment, and "Not Preventable" as per Preventability Assessment.

INTRODUCTION: Nowadays, Noncommunicable diseases (NCDs), are responsible for the majority of global deaths, and cancer is expected to rank as leading cause of death and the single most important barrier to increasing life expectancy in every country of the world in the 21st century [1].

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Among the multimodal approaches for the treatment of cancer, Chemotherapy is widely used with regimens being complex; patients are more susceptible to adverse drug reactions with little tolerance due to low immunity [2].

As defined by World Health Organisation, adverse drug reaction (ADR) is any noxious or unintended response to a drug, which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function [2]. The ADRs due to cancer chemotherapy would affect the patient economically and clinically as it leads to hospitalization, prolongation of

hospital stay, and emergency hospital visits [3]. The prevalence of ADRs of anticancer drugs in India is 10-12% [2].

World Health Organization defined pharmacovigilance as the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any drug-related problem (WHO, 2002). Therefore, Pharmacovigilance in oncology branch is highly essential for safe and effective medications [2].

The studies regarding pattern ADRs in cancer chemotherapy patients are few in India, a similar scenario is found at local and regional levels also. So, a study was planned to analyze causality, severity, and preventability of various adverse drug reactions (ADRs) at the cancer institute of a tertiary care teaching hospital, Gujarat, India, for one year. The analysis was considered to provide opportunities for interventions, especially for the preventable ADRs, to promote safer drug use. The observations made, if disseminated to other healthcare professionals, may help improve the quality of patient care by ensuring safer use of drugs. Finally, similar reporting exercises may become necessary to educate and to increase the awareness about ADRs to all the concerned patients.

Aims and Objectives:

- To study Adverse Drug Reactions (ADRs) due to anti-cancer drugs in patients coming to the oncology department.
- To assess the causality of various adverse drug reactions using the Naranjo's probability scale, severity grading using modified Hartwig and Siegel scale, and preventability analysis using modified Schumock and Thornton scale.

MATERIALS AND METHODS:

Study Site: This study was carried out in oncology department at a tertiary care teaching hospital, Gujarat, India.

Study Design: This was a cross-sectional, observational study that was aimed to evaluate the adverse drug reactions of anticancer drugs used in cancer treatment.

Study Duration: This study was carried out for a period of one year after getting approval from Institutional Ethics Committee.

Study Criteria: Patients on cancer chemotherapy attending the oncology department were enrolled for the study as per inclusion criteria.

Inclusion Criteria:

1. Patients of either sex and age group on anticancer drugs.
2. Patients willing to give consent for the study

Exclusion Criteria:

1. Adverse drug reaction due to other drugs, blood transfusion, patients with a history of drug abuse and intoxications [4].

Study Approval: The research protocol was approved by Institute Human Research Ethics Committee (No. GMCS/STU/ETHICS/Approval/ 160/19) before starting the study.

Study Procedure: After obtaining informed consent, data on ADRs of anticancer drugs were collected of cancer patients diagnosed by a concerned clinician from the oncology department. No change in the treatment decision, schedule, or duration of cancer chemotherapy was made as a part of the study.

The causality of ADRs due to suspected medications was assessed using Naranjo's probability scale, which is a questionnaire that contains 10 objective questions with three types of responses – yes, no, or do not know.[3] The severity of the ADRs was assessed using modified Hartwig and Siegel scale, which classifies ADRs into "mild," "moderate, "or "severe" with various levels, depending on factors like a requirement for change in treatment, duration of hospital stay and the disability produced by the ADR.[2] 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 [3].

Descriptive statistics were applied by using MS Excel.

RESULTS: A total number of 683 reports were received from 198 patients during the study period that met the inclusion/exclusion criteria of the study. Among these 198 patients, 64.14% of the enrolled patients were females, and 35.85% were males.

Various anticancer agents were prescribed to the patients, which include individual chemotherapeutic agents and drug regimens. Frequency of anticancer agents include:

Chemotherapeutic agents used individually were Cisplatin (68%) followed by Paclitaxel (15%), Docetaxel (6%), Gemcitabine (5%), Zoledronic acid (2%), Gefitinib (1%), Capecitabine (1%), Carboplatin (1%) **Table 1A.**

Chemotherapeutic drug regimens used were Paclitaxel + Carboplatin (29%), followed by Adriamycin (Doxorubicin) + Cyclophosphamide (21%), Gemcitabine + Carboplatin/Cisplatin (5%), and rest of the drug regimens used are shown in **Table 1B.**

TABLE 1A: INDIVIDUAL CHEMOTHERAPEUTIC AGENTS USED IN CARCINOMA

Individual drug name	Frequency (n=85)	Percentage (%)
Cisplatin	58	68%
Paclitaxel	13	15%
Docetaxel	5	6%
Gemcitabine	4	5%
Zoledronic acid	2	2%
Gefitinib	1	1%
Capecitabine	1	1%
Carboplatin	1	1%

TABLE 1B: CHEMOTHERAPEUTIC DRUG REGIMENS USED IN CARCINOMA

Drug regimens	Frequency (n=143)	Percentage (%)
Paclitaxel + Carboplatin	42	29%
Adriamycin (Doxorubicin) + Cyclophosphamide	30	21%
Gemcitabine + Carboplatin	7	5%
Gemcitabine + Cisplatin	7	5%
Paclitaxel + Cisplatin + 5-Fluorouracil	6	4%
Cisplatin + Etoposide + Bleomycin	4	3%
Pemetrexed + Carboplatin	4	3%
Paclitaxel + Ifosphamide + Cisplatin	4	3%
Cisplatin + 5-Fluorouracil	4	3%
Gemcitabine + Docetaxel	3	2%
Cisplatin + Etoposide	3	2%
Docetaxel + Cyclophosphamide	3	2%
Carboplatin + Etoposide	2	1%
Adriamycin (Doxorubicin) + Vinblastine + Dacarbazine + Bleomycin	2	1%
Ifosphamide + Adriamycin (Doxorubicin)	2	1%
Epirubicin + Cyclophosphamide	2	1%
Oxaliplatin + Capecitabine	2	1%
Adriamycin (Doxorubicin) + Vincristine + Cyclophosphamide + Prednisolone	1	1%
Irinotecan + Calcium Leucovorin + 5-Fluorouracil	1	1%
Docetaxel + Carboplatin	1	1%
5-Fluorouracil + Epirubicin + Cyclophosphamide	1	1%
Cisplatin + Adriamycin (Doxorubicin)	1	1%
Etoposide + Ifosphamide	1	1%
Adriamycin (Doxorubicin)+ Cyclophosphamide + 5-Fluorouracil	1	1%
Paclitaxel + Cisplatin	1	1%
Bicalutamide + Zoledronic acid	1	1%
Docetaxel + Carboplatin + Zoledronic acid	1	1%
Methotrexate + 5-Fluorouracil	1	1%
Vincristine + Cyclophosphamide + Prednisolone	1	1%
Docetaxel + Cisplatin + 5-Fluorouracil	1	1%
Rituximab + Bendamustine	1	1%
Paclitaxel + Carboplatin + 5-Fluorouracil	1	1%
Docetaxel + Zoledronic acid	1	1%

Among overall clinical manifestations of the reported ADRs, it was found that 21.08% of ADRs were of alopecia, 17.27% nausea/vomiting, followed by 11.56% nail pigmentation, and the rest of the ADRs found are shown in **Fig. 1**.

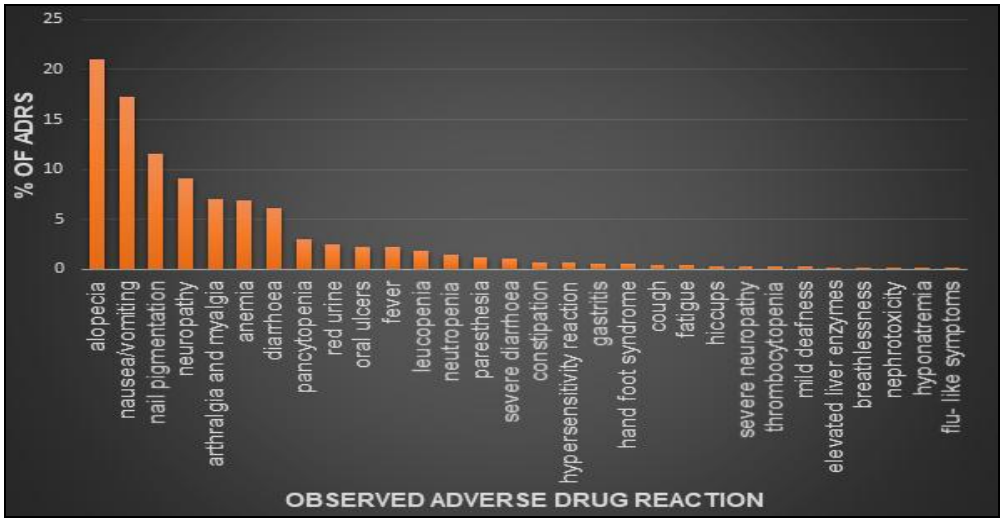

FIG. 1: CLINICAL MANIFESTATIONS OF THE REPORTED ADRS

TABLE 2A: HEMATOLOGICAL ADRS

Hematological ADRs	Frequency (n=93)	Percentage (%)
anemia	47	50.53
pancytopenia	21	22.58
leucopenia	13	13.97
neutropenia	10	10.75
thrombocytopenia	2	2.15

Major Hematological ADRs found were anemia (50.53%), pancytopenia (22.58%), followed by leucopenia (13.97%), neutropenia (10.75%), thrombocytopenia (2.15%) **Table 2A.**

Major Non-Hematological ADRs found were alopecia (24.4%), nausea/vomiting (20%), nail pigmentation (13.38%), neuropathy (10.5%), rest of the non-hematological ADRs found are shown in **Table 2B.**

TABLE 2B: NON-HEMATOLOGICAL ADRS

Non-Hematological ADRs	Frequency (n=590)	Percentage (%)
alopecia	144	24.4
nausea/vomiting	118	20
nail pigmentation	79	13.38
neuropathy	62	10.5
arthralgia and myalgia	48	8.13
diarrhoea	42	7.11
red urine	17	2.88
oral ulcers	15	2.54
fever	15	2.54
paresthesia	8	1.35
severe diarrhoea	7	1.18
constipation	5	0.84
hypersensitivity reaction	5	0.84
gastritis	4	0.67
hand foot syndrome	4	0.67
cough	3	0.5
fatigue	3	0.5
hiccups	2	0.33
severe neuropathy	2	0.33
mild deafness	2	0.33
elevated liver enzymes	1	0.16
breathlessness	1	0.16
nephrotoxicity	1	0.16
hyponatremia	1	0.16
flu- like symptoms	1	0.16

Adverse drug reactions in individual chemotherapeutic agents- The maximum ADRs are observed with Paclitaxel followed by Cisplatin and Gemcitabine, minimum ADRs with Capecitabine, and Carboplatin **Fig. 2.**

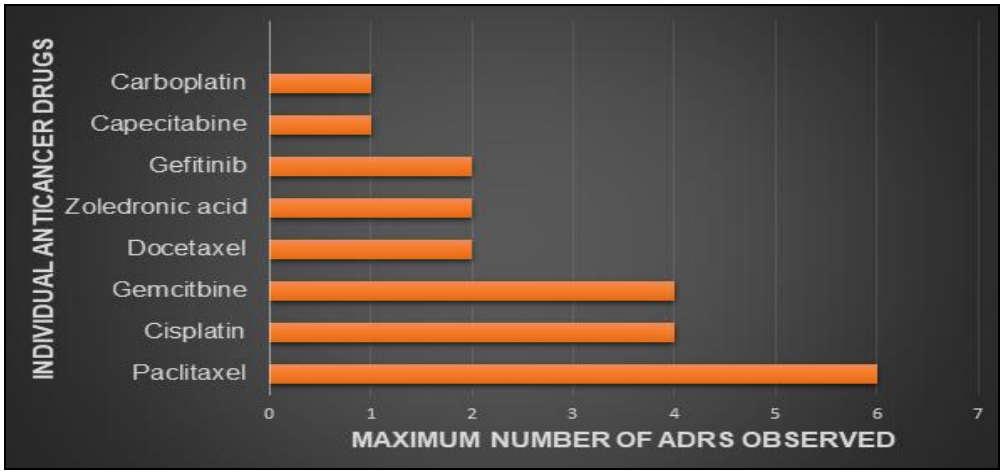

FIG. 2: ADRS IN INDIVIDUAL CHEMOTHERAPEUTIC AGENT

Adverse drug reactions in chemotherapeutic drug regimens- The maximum ADRs found with regimen having Paclitaxel + Carboplatin followed by Cisplatin + Etoposide + Bleomycin and Paclitaxel + Ifosphamide + Cisplatin **Table 3**.

TABLE 3: ADRs IN CHEMOTHERAPEUTIC DRUG REGIMENS

Drug regimens	Highest no. of ADRs found
Paclitaxel + Carboplatin	8
Cisplatin + Etoposide + Bleomycin	6
Paclitaxel + Ifosphamide + Cisplatin	6
Adriamycin (Doxorubicin) + Cyclophosphamide	5
Gemcitabine + Carboplatin	5
Paclitaxel + Cisplatin + 5-Fluorouracil	5
Gemcitabine + Docetaxel	5
Carboplatin + Etoposide	5
Cisplatin + Etoposide	5
Adriamycin (Doxorubicin) + Vinblastine + Dacarbazine + Bleomycin	5
Ifosphamide + Adriamycin (Doxorubicin)	5
Adriamycin (Doxorubicin) + Vincristine + Cyclophosphamide + Prednisolone	5
Pemetrexed + Carboplatin	4
Irinotecan + Calcium Leucovorin + 5-Fluorouracil	4
Cisplatin + 5-Fluorouracil	4
Docetaxel + Carboplatin	4
Gemcitabine + Cisplatin	4
5-Fluorouracil + Epirubicin + Cyclophosphamide	4
Cisplatin + Adriamycin (Doxorubicin)	4
Etoposide + Ifosphamide	4
Adriamycin (Doxorubicin)+ Cyclophosphamide + 5-Fluorouracil	4
Paclitaxel + Cisplatin	4
Epirubicin + Cyclophosphamide	3
Bicalutamide + Zoledronic acid	3
Docetaxel + Carboplatin + Zoledronic acid	2
Methotrexate + 5-Fluorouracil	2
Docetaxel + Cyclophosphamide	2
Oxaliplatin + Capecitabine	2
Vincristine + Cyclophosphamide + Prednisolone	2
Docetaxel + Cisplatin + 5-Fluorouracil	2
Rituximab + Bendamustine	2
Paclitaxel + Carboplatin + 5-Fluorouracil	1
Docetaxel + Zoledronic acid	1

The causality assessment of the ADRs using the Naranjo's probability scale showed Possible (49.34%) followed by Probable (47.58%), Doubtful (3.07%) with hardly any ADR in Definite group **Fig. 3**.

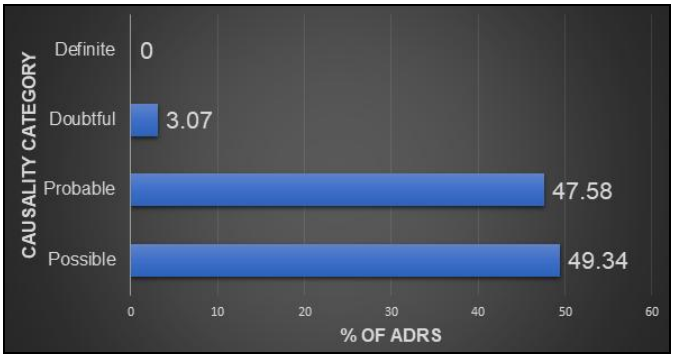

FIG. 3: CAUSALITY ASSESSMENT BY THE NARANJO'S PROBABILITY SCALE

Severity grading by modified Hartwig and Siegel scale showed Mild (91.21%) followed by Moderate (8.05%) and Severe (0.73%) **Fig. 4**.

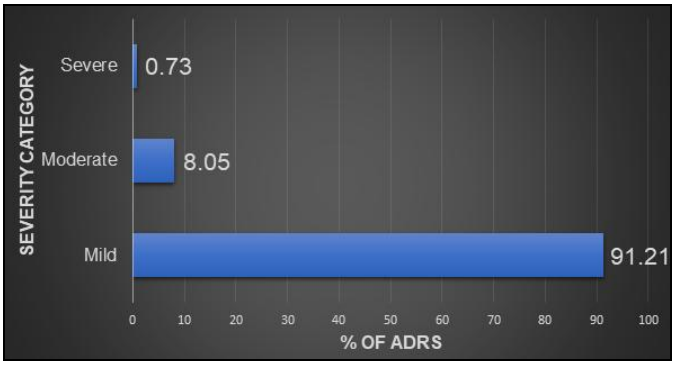

FIG. 4: SEVERITY GRADING BY MODIFIED HARTWIG AND SIEGEL SCALE

The analysis of the preventability of ADRs according to modified Schumock and Thornton scale showed Not Preventable (57.83%) followed by Probably Preventable (24.3%) and Definitely Preventable (17.86%) **Fig. 5**.

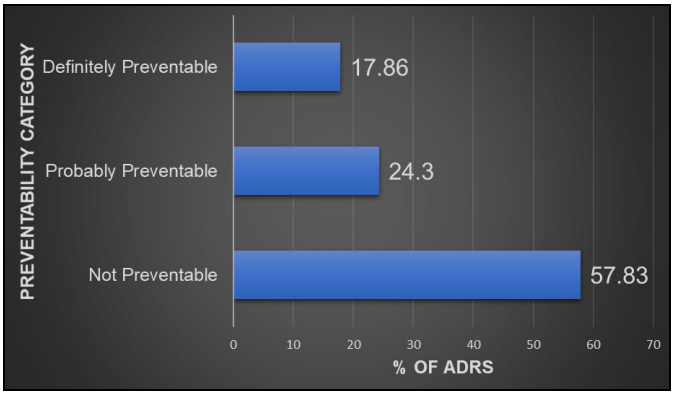

FIG. 5: PREVENTABILITY ANALYSIS BY MODIFIED SCHUMOCK AND THORNTON SCALE

DISCUSSION: Cancer is defined as a multi-cellular disease which can arise from any cell type and organ.4 Cancer has now become a global burden and is one of the major causes of mortality in developing countries. This is due to rapid globalization and insalubrious lifestyles, and the acceptance of many features of a western dietary pattern, thus causing the higher occurrence of cancer in such countries [3]. The incidence of cancer is increasing in India. Around 2.5 million people live with cancer in India. Over seven lakh new patients register every year, and cancer mortality is around 5,56,400 in a year [5].

There are many treatment modalities for the treatment of cancer. Amongst them, chemotherapeutic agents are highly beneficial in oncology therapy, but they are used with vigilance in view of considerable toxicity and narrow therapeutic window. The spectrum of Adverse Drug Reactions (ADRs) associated with them has become more diverse that impairs the quality of life, decreases the work productivity of patients [3, 6].

Studies regarding the pattern of adverse drug reactions (ADRs) in cancer chemotherapy patients are scarce in India. So, this study was conducted to systematically explore the safety profile of anticancer drug use and generate baseline data by assessing the adverse drug reactions due to cancer chemotherapy in daycare patients of carcinoma coming to the oncology department of a tertiary care teaching hospital Gujarat, India. This cross-sectional, observational study was conducted for a period of one year. A total number of 683 reports were received from 198 patients during this study period that met with the inclusion/exclusion criteria of the study.

From the total ADRs received in the study, it was found that 64.14% of the enrolled patients were females, and 35.85% were males. Similar results were reported by Rout A *et al*., Sowmya MS *et al*. and Behera *et al.* [2, 4, 7] A review of 48 cohort studies in UK by Martin *et al.*, showed that ADRs are more commonly observed in females than males, which was attributed to increased consulting rates for women compared to men in these studies [8]. This is in contrast to the study by Sunil Bellare *et al.* and Prasad *et al.*, where ADRs were more observed in male patients [9, 10]. More number of ADRs were observed in females due to alteration in pharmacokinetics and pharmacodynamic of the drug due to hormonal changes [11, 12].

In view of various anticancer drugs used in the present study, chemotherapeutic agents used individually were Cisplatin (68%) followed by Paclitaxel (15%), Docetaxel (6%), Gemcitabine (5%), *etc*. **Table 1A.** This is similar to drugs used in study done by Chatterjee *et al*. [13] Antimetabolites and alkylating agents were found to be the commonest antineoplastic drugs in a study by Poddar *et al*. [14] Chemotherapeutic drug regimens used were Paclitaxel + Carboplatin (29%), followed by Adriamycin (Doxorubicin) +Cyclophosphamide (21%), Gemcitabine + Carboplatin/Cisplatin (5%), *etc*. **Table 1B**.

Cancer chemotherapy damages rapidly dividing cells of bone marrow resulting in myelosuppression, thus affecting white blood cells, platelets, and red blood cells, which leads to a lowering of immunity, and so patients on cancer chemotherapy are at high risk for developing various infections. Nausea and vomiting are prominent with most cytotoxic agents and is caused mainly due to direct stimulation of chemoreceptor trigger zone [15].

In the present study, most of the adverse drug reactions were observed affecting the gastrointestinal system, followed by the hematological system **Fig. 1**. These findings were quite similar to the study of Chopra *et al.,* [16] Contrary to the present study Mallik *et al.,* observed that adverse drug reaction affecting the hematological system was commonly followed by the gastrointestinal system [17]. Commonest ADR was found to be alopecia (21.08%) followed by nausea/vomiting (17.27%), nail pigmentation (11.56%), neuropathy (9.07%) **Fig. 1**. These findings are similar to studies by Kaur *et al.,* Poddar *et al.,* and Lakshmi *et al.,* which showed an incidence of alopecia to be 27.76%, 58%, and 95%, respectively [14, 18, 19]. But studies by Prasad et al, Chopra *et al*. and Swathi *et al*. showed nausea and vomiting as the most common adverse drug reactions observed in 33.33%, 25.5%, and 46% of the total ADRs, respectively [10, 16, 20]. Studies carried out by Mallik *et al.* reported neutropenia as the most common ADR, while a study conducted by Lau *et al.* reported constipation to be the commonest ADR [17, 21]. Hyperpigmentation is a frequent side effect of many drugs. Certain chemotherapy drugs like Bleomycin, Etoposide, Cyclophosphamide, Carboplatin, Hydroxyurea, Capecitabine, Melphalan, and 5-FU can cause hyperpigmentation of the skin as a side effect [22]. A case report by Kumar *et al.* showed an unusual pattern of nail pigmentation following a Cyclophosphamide-containing chemotherapy regimen in a 60-year-old female patient with breast cancer.23 It was found that L-asparaginase (L-Asp)-based chemotherapy regimen when used in patients of acute lymphoblastic leukemia ALL) produces more incidences of hypoglycemia than hyperglycemia, thus showing the abnormal change in plasma glucose levels [24]. A study done by Anwikar *et al.,* showed that there is a possibility of tetany by bevacizumab, which may occur by interfering with calcium metabolism [25].

In the present study, the highest ADRs observed when the individual drug was used with Paclitaxel, followed by Cisplatin and Gemcitabine **Fig. 2.** When drug regimens were used, the highest ADRs were observed with Paclitaxel + Carboplatin followed by Cisplatin + Etoposide + Bleomycin **Table 3**. This is in accordance with reports from other similar studies done by Prasad *et al.,* Mallik *et al.,* and Swathi *et al.* [17, 20] In a study by Mugada *et al.,* monotherapy with Paclitaxel was found to have highest number of ADRs. 5-FU + Cisplatin combination therapy had highest number of ADRs followed by Doxorubicin + Cyclophosphamide and Doxorubicin + Cyclophosphamide + 5-FU.[26] ADRs were found to be maximum with alkylating agents and the least with hormonal agents in a study done by Reji *et al.* [27]

Causality assessment of ADRs is the standardized and detailed assessment of individual case safety reports for the likelihood of involvement of the suspected drug/s in causing the particular ADR. The basic knowledge of causality assessment is indispensable for healthcare professionals as the uncertainty of the potential causal relationship between drugs and ADR remains one of the major reasons of under-reporting in pharmacovigilance.[28] In the present study, the causality assessment was carried out using the Naranjo's probability scale. 49.34% of the ADRs came in the category of Possible, 47.58% ADRs were Probable. 3.07% ADRs were Doubtful. There were no "Definite" reactions as re-challenge was not attempted in any of the patients **Fig. 3**. This-findings were similar to

studies were done by Chopra *et al.* and Swathi *et al.* [16, 20] . In contrast, most of the ADRs were Probable in a study by Sharma *et al.* [15]

The grading of severity of ADRs was done according to the modified Hartwig and Siegel scale. It was found that most of the reactions were of Mild to Moderate severity, and thus it did not warrant stoppage or changing of the drug. Similar studies can be used to identify iatrogenic adverse effects and may help in preventing such occurrences in the future. Out of the total ADRs received, it is evident that 91.21% of ADRs were mild in severity, 8.05% of ADRs were moderate in nature. Only 0.73% of Severe ADRs were seen in the present study **Fig. 4**. This is comparable to the study done by Chopra et al.[16] . However, a study by Sharma *et al.* and Swathi *et al.* showed that most of the ADRs were Moderate in nature [15, 20].

The analysis of the preventability of ADRs was done according to the modified Schumock and Thornton scale. Out of the total ADRs received, it is evident that 57.83% of ADRs were Not Preventable, 24.3% ADRs were Probably Preventable. Only 17.86% belonged to the Definitely Preventable group **Fig. 5**. Studies done by Rout *et al.* and Sharma *et al.* showed similar results [2, 15]. Whereas, majority ADRs were found to be Definitely Preventable in a study done by Swathi *et al.* [20]

Thus, the study provides basic information regarding the safety profile of various anticancer drugs in different types of cancers. Assessment of three different parameters of the ADR was noted, namely the causality, severity, and preventability. Other studies have focused on either a single drug or only on the causality aspect [10, 17, 29].

LIMITATION: It was observed that most of the ADRs were of "Not Preventable" type as per analysis by preventability assessment scale because most of the points of the scale-like laboratory monitoring test, drug interaction, compliance, could not be measured.

CONCLUSION: In our study, among overall clinical manifestations of the reported ADRs, it was found that 21.08% of ADRs were of alopecia, 17.27% nausea/vomiting, followed by 11.56% nail pigmentation. The maximum ADRs found with Paclitaxel and Paclitaxel + Carboplatin. Causality assessment showed possible category maximum, severity grading showed Mild level maximum, and preventability analysis showed Not Preventable category maximum. The analysis of the adverse drug reactions with an assessment of causality, severity, and preventability showed the importance of Pharmacovigilance in cancer chemotherapy. Regular monitoring and reporting will decrease the occurrence of ADRs, increase patient compliance, reduce morbidity and mortality, and also a financial burden for the patients and society. By spreading awareness among the treating physicians and training of the health care personnel will help in the early diagnosis of adverse drug reactions and their prompt management.

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CONFLICTS OF INTEREST: None declared

ETHICAL APPROVAL: The Institutional Ethics Committee approved the study (No. GMCS/ STU/ETHICS/Approval/160/19)

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