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Original Article

Prospective Observational Study of Adverse Drug Reactions of Anti-HER2 and Microtubule Damaging Drugs Used in Cancer Treatment in a Tertiary Care Hospital

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ABSTRACT

Background: Cancer treatment has witnessed remarkable advancements with the development of targeted therapies, such as anti-HER2 agents and microtubule-damaging drugs. Despite their efficacy, these drugs can be associated with a spectrum of Adverse Drug Reactions (ADRs) that may impact patient safety and treatment outcomes. Data on the safety profile of cancer treatment are scarce. **Aim:** This prospective observational study aimed to systematically assess and characterize adverse drug reactions related to anti-HER2 and microtubule-damaging drugs in the clinical setting of a tertiary care hospital. **Materials and Methods:** We conducted a comprehensive observational study over a specified period involving patients undergoing cancer treatment with anti-HER2 and microtubule-damaging drugs. A structured data collection process was employed to record patient demographics, treatment regimens, and observed adverse drug reactions. The severity of adverse drug reactions was categorized according to well-established criteria. The data was analyzed using frequency distribution association analysis to identify potential risk variables for adverse drug reactions. **Results and Discussion:** Preliminary results from our study displayed an extensive array of adverse drug events associated with anti-HER2 and microtubule-damaging drugs, including cardiotoxicity, neuropathy, and myelosuppression. The degree of incidence and impact of adverse drug reactions varied depending on both patient medications and their variables. Furthermore, certain risk factors, such as age, comorbidities, and concomitant medications, were identified as potential predictors of adverse drug reactions. **Conclusion:** This prospective observational study provides valuable insights into the incidence, patterns, and risk factors of ADRs related to anti-HER2 and microtubule-damaging drugs in cancer treatment. The findings will aid healthcare professionals in optimizing treatment strategies, monitoring patients effectively, and managing adverse drug reactions, ultimately providing high-quality care to patients in a tertiary hospital. Advanced research and continuous surveillance are essential to enhance our understanding of these adverse drug reactions and develop strategies for their prevention and management.

Keywords: Adverse drug reactions, Quality, Safety profile on cancer treatment, Patient care.

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INTRODUCTION

More than a century of tragic events involving drug availability have significantly impacted the procedures and mechanisms used in drug development.[1] A century's horrible occurrences have deeply impacted the structures and processes utilized in pharmaceutical development today, none more so than Pharmacovigilance (PVA).[2] Since some ADRs do not fall under type A or type B, other categories have been created. These include types C, D, E, and reactions.[3]

Causality Assessment Tools for ADR

Investigating and reporting adverse drug reactions is essential for pharmacovigilance and clinical research. The Naranjo scaling scheme is one of the methods for determining causality that is most frequently applied.[4] An adverse reaction can be evaluated by using the Naranjo method. This evaluation comprises ten questions about the medicine issued and the response phenotype. There are point values associated with each of the three possible responses to each question: "Yes," "No," or "Unknown".[5] Each correctly answered question is assigned a unique rating, which is then summed to get a final rating corresponding to one of four likelihood categories (unlikely, possibly, probably, or definitely) that the medication was the cause of the reaction.[6] Despite being recorded in the Electronic Medical Record (EMR), the data often lack the information a physician needs to decide how to prescribe

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medications safely. Key factors such as phenotype and severity of adverse effects must be determined to ensure efficacy, as many side effects are tolerable with low risk. In contrast, others can be severe and potentially fatal.[7] Hartwig's Severity Assessment Tool[8] is the foundation for severity classification. With one exception, if the medication in question is stopped, we now classify the response as mild.[7]

Clinical pharmacists who undergone pharmacovigilance training gather additional information on the ADR traits, ADR treatment, assessment of the Naranjo scale, and if an adverse event happened within 30 days of assessment. According to research, Adverse Drug Reactions (ADRs) greatly raise healthcare costs.[9] ADRs can occasionally be expensive to treat, and the morbidity and mortality they cause outweigh the actual treatment cost.[10] Because of the major advances in medical research, cancer treatments today-including those for testicular, lymphoma, and leukemia-are curative rather than palliative. Chemotherapy is a particular aspect of a diverse approach to treat malignancies.[11]

The immediate consequences of frequently used anti-carcinogenic medications include nausea and vomiting attributed to a critical mechanism, which may sometimes be rather uncomfortable.[12] Malignant cells are more sensitive or recover less efficiently than normal cells, making anti-neoplastic therapy possible. The therapeutic activity of anti-neoplastic therapy, which affects all rapidly dividing cells and does not prefer malignant cells, is an extension of many side effects.[12] ADRs from chemotherapy for cancer are common. Myelosuppression, mucositis, and other Adverse Drug Reactions (ADRs) frequently occur during cancer treatment.[13] Chemotherapy may be less effective for cancer patients if doses are delayed or reduced while keeping the same dose intensity. Their effectiveness and toxicity can be significantly influenced by the dose regimen and administration technique.[14] Data on the safety profile of cancer treatment are scarce. The current research investigation aimed to analyze adverse drug effects in patients undergoing chemotherapy with MTDD and anti-Her2 drugs at CyteCare Hospital in Yelahanka, Bangalore, a tertiary care facility.

MATERIALS AND METHODS

This research is a prospective cohort study of the adverse effects of anti-HER-2 derivative (Trastuzumab) and microtubule-damaging drugs (taxanes and vinca alkaloids) done from July 2023 to September 2023. The study was carried out at CyteCare Hospital in Yelahanka, Bengaluru. The consent form met the ethical standards. Prior to enrolling patients (or their relatives) in the study, a thorough explanation was given, and informed consent was obtained from them. The patients admitted in both day-care and inpatients receiving chemotherapy were included. A sample size of 150 information pertaining to patients was obtained using an effectively designed data collection form that included patient socioeconomic data as shown in Figure 2, therapy charts, and drug assessment reports, and the patient was monitored daily till the day of discharge. The patient medication chart was reviewed daily for any adverse events. On the basis of inclusion and exclusion criteria, patients were included for the study as specified below.

Study site

This study is conducted in CyteCare Hospital, Yelahanka, Bangalore.

Study criteria

Inclusion criteria

The study's population includes all patients over the age of 18 who had been diagnosed with HER2-positive breast cancer and were receiving anti-carcinogenic medications as individual drugs or with many drugs. This research included the patient's receiving treatment with microtubule inhibitors (taxanes and vinca alkaloids) and anti-HER2 (Trastuzumab) drugs.

Exclusion criteria

Cancer patients who denied to participate were not included in this research study. Patients who were receiving chemotherapy that did not include microtubule-damaging agents like taxanes and vinca alkaloids, anti-HER2 (Trastuzumab) drugs were also included. Additionally, patients who experienced adverse drug reactions due to other causes such as blood transfusions, those with a history of drug misuse, and those who had been intoxicated, were excluded from the study.

Source of data

Information received from a physician, laboratory data and patient treatment chart.

Collection of data and subsequent follow-up

Data were collected from the patients selected for the study till September 2023, and all those who met the criteria were monitored for a period of three months after they started medication. Once the patients were enrolled, the study collected demographic, clinical, and therapy information in a precisely created data form. The clinical details included diagnosis, baseline vital signs, associated comorbidities during presentation in the outpatient department, cytopathology, radio imaging, and hematological data from the baseline laboratory test. The study documented the prescribed treatment regimen, the drug dosage, the frequency and mode of administration, and the date when chemotherapy was started. During following visits and hospital stays, all patients were followed up with physical tests such as temperature, pulse, blood pressure, and other tests taken during hospitalization.

Study design

This study was carried out in both day-care and inpatients receiving chemotherapy. Patients who met the eligibility requirements were notified, and only those interested patients were included after receiving consent from them. The data needed were obtained in a effectively designed data collecting form (which included patient socioeconomic information, therapy charts, and medication assessment reports), and the patient was monitored daily till the day of discharge. The patient medication record was reviewed daily for any adverse events. The casualty evaluation of the recorded ADR was conducted utilizing the "Naranjo causality assessment scale." The Naranjo Algorithm classifies pharmacological reactions as definite, likely, or potential.

Sample size and Duration of study

150 patients were included in this study. The present research was done for a minimum duration from July 2023 to September 2023.

Table 1: Patients showing adverse drug reactions after chemotherapy with MTDD and anti-Her2 agents.

Patients	Number
Patients receiving chemotherapeutic agents.	150
Patients developing adverse drug reactions.	131
Percentage of patients developing adverse drug reactions.	87.33%

Data collection

The researcher used the Adverse Drug Reaction Monitoring form created by the Centre for Drug Standard Control Organization (CDSCO) to obtain information related to Adverse Drug Reactions (ADRs). In addition, a separate questionnaire was developed and utilized to collect social and demographic information as shown in Table 2.

Causality evaluation for adverse drug events

It involves investigating the connection of causality between a suspected medication and the undesirable effect in challenge. The WHO causality assessment scale divides causality into six categories as follows: "certain," "probable," "possible," "unlikely," "conditional/ unclassified," and "unassessable/unclassifiable".[15] Furthermore, the degree of severity of the adverse drug reaction is categorized by employing the modified Hartwig and Siegel scale, which classifies severity as "mild," "moderate," or "severe" according to factors like the necessity for a change in therapy, the length of the hospitalization, and impairment caused by the ADR.[16] Finally, the modified Schumock and Thornton scale is utilised to identify the uncertainty of an ADR, which is classified as "definitely preventable," "probably preventable," or "not preventable."[17]

Statistical Analysis

After the data was obtained, it was validated. This resulted in a clean datasheet that was subsequently copied into SPSS

Table 2: Socio Economic Variation of patients.

Variable		Number	Percentage *n*=150
	Male	28	18.66
Sex	Female	122	81.33
	0-18	8	5.33
	18-45	47	31.33
Age	45-65	64	42.66
	65-75	23	15.33
	75-100	8	5.33
	Upper	26	17.33
	Upper middle	41	27.33
Socio economic status	Lower middle	23	15.33
	Upper lower	49	32.66
	Lower	11	7.33
Marital Status	Married	131	87.33
	Unmarried	17	11.3
	Widow	2	1.33

*Modified Kuppuswami scale evaluated the social and economic status of research participants.

for analysis. Finally, the casualty assessment of adverse drug reactions was done using SPSS, a statistical program designed for quantitative data analysis

RESULTS

In the study period (July-September), 150 patients who received chemotherapeutic agents to treat their malignant conditions participated in the study period with reference to the inclusion and exclusion criteria and were monitored thoroughly till the completion of the study. Because alopecia only has psychological and social consequences, this negative effect was nonetheless included in the present investigation. Our current research focuses on the harmful response of drugs that occur in patients treated with taxanes, vinca alkaloids, and anti-HER2 drugs (Table 1).

Gender Vs Total Patients

Out of 150 patients, 28 (18.6%) were men, while the remaining 122 (81.3%) were women as shown in Figure 1.

The age distribution showed that 61 patients (40.6%) were between the ages of 45 and 65, with only eight (5.33%) being under the age of 18. 46 (30.6%) patients were between the ages of 18 and 45, 23 (15%) between the ages of 65 and 75, and 7 (4.6%) were 75 years or older. At the period of admission to the hospital, 131 patients (87.33%) were already married, 2 (1.33%) were widowed, and 17 (11.3%) had never married. Figure 2 shows the demographic and socioeconomic details of the research's participants.

The modified Kuppuswami scale was used to measure the patients' socioeconomic standing, which revealed that 18% of them had an upper socioeconomic status and another 27.33% were in the upper-middle income group. The majority of the sample population (34%) had an upper-lower socioeconomic category, while 14.66% belonged to the two lower middle-class groups. The male-female ratio was 2:9, with 28 males and 122 females. Notably, the 45-65 age group had the maximum number of patients, accounting for 40.67% of the total number of patients who participated in this research study as shown in Figure 2.1

Figure 3 represents the distribution pattern of different cancers within the study population. The cancer of the breast was the most prevalent malignancy in this study, followed by ovarian carcinoma. Ovarian cancer was diagnosed in fifteen patients each. Four patients were diagnosed with esophageal, lung, and tongue carcinomas, and one patient was identified with prostate cancer. Bladder carcinoma, testicular cancer, and Chronic Myeloid Leukemia (CML) were seen in two patients each. Four patients developed Acute Myeloid Leukemia (AML), endometrium cancer, Non-Hodgkin's lymphoma (NHL), and tongue carcinoma, respectively. DLBCL and follicular lymphoma were found in five cases. Only one patient had tonsils, stomach, prostate, and Ewings sarcoma.

Figure 3.1 illustrates different Anti-Cancer agents used in the study population. The most common adverse effects among patients were anemia and diarrhoea, which occurred in six people. The next observed adverse effect was found to be candidiasis

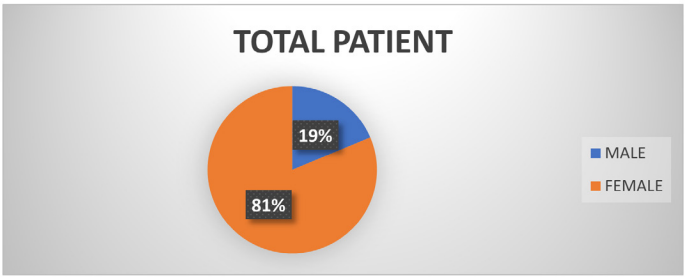


Figure 1: Distribution pattern of gender vs total patients.

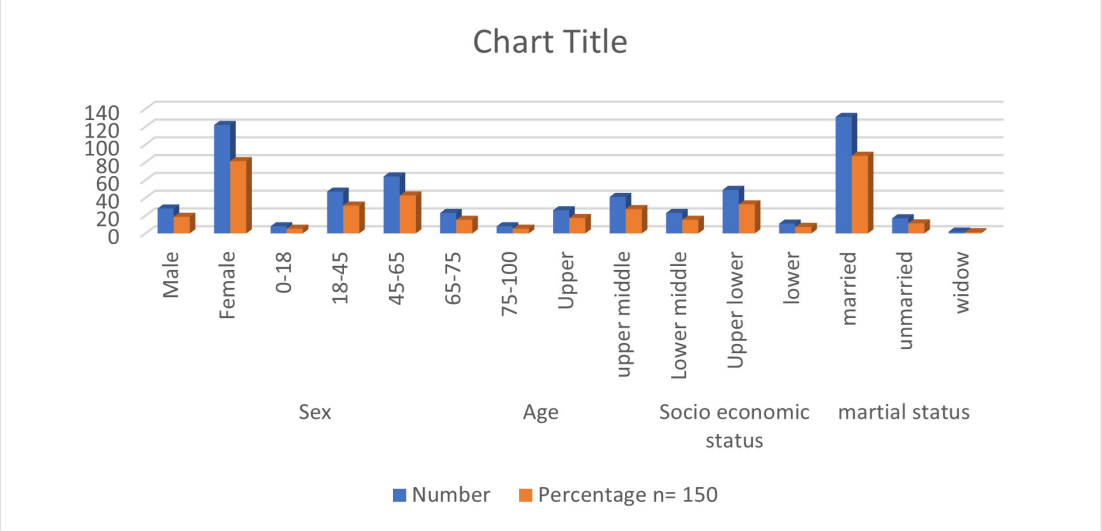


Figure 2: Demographic information of patients.

reported by five patients. Other adverse drug reactions were reported less frequently. Four patients developed candidiasis and febrile neutropenia, while two experienced neuropathy and vomiting. Many patients reported thrombocytopenia, cellulitis, angular stomatitis, photodermatitis, symptomatic hyponatremia, and hypersensitivity as a single adverse reaction.

According to Table 3, the most common drug regimens that caused adverse drug reactions (ADRs) were Platinum Compound (13.63%), followed by R-CHOP (9.09%), Carbotaxol+Herceptin (11.36%), T-DM1+Taxol (9.09%), Carbotaxol (13.63%), TCH (13.63%), VDP (6.81%), and Pacliaqualip (6.81%). It is noteworthy that antibiotics like bleomycin and doxorubicin, Platinum compounds like carboplatin, antimetabolites and nitrogen mustard were also among the drugs that reported different adverse drug reactions in the patients during treatment.

Figure 4 illustrates the incidence of adverse drug reactions in patients with anti-Her2 and microtubule agents (vinca alkaloids and taxane derivatives).

Causality, Severity, and Preventability Assessment

Based on WHO-UMC standards, the causality, severity, and preventability evaluations were done and revealed that 37 (84.09%) were probable and 8 (18.18%) were plausible adverse events in the study. Rechallenge was not performed on any of the patients; hence no particular ADR was found. The degree of severity of the ADRs reported was assessed using the modified Hartwig and Siegel Scale. The maximum of the ADRs reported was moderate 35 (79.54%), followed by mild in 9 (20.45%) of the patients. Only 1 (2.27%) of the ADRs were severe. According to the modified Schumock and Thorton scale, maximum ADRs 35 (79.54%) were not preventable. 3 (6.81%) were definitely preventable, and 6 (13.63%) were probably preventable, more details in Table 4.

DISCUSSION

This research study evaluated the pattern and severity of adverse drug reactions at CyteCare Hospital, Bangalore for patients who were treated with different anti-cancer regimens. Of 150 patients

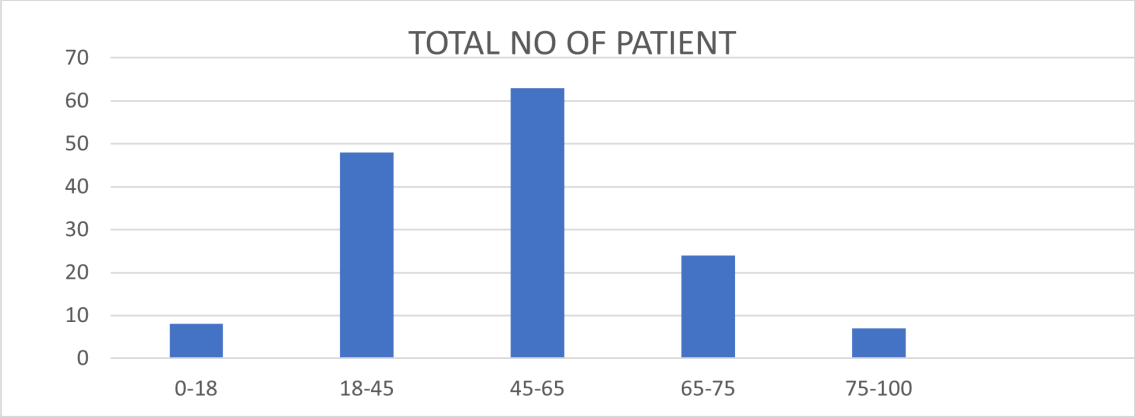
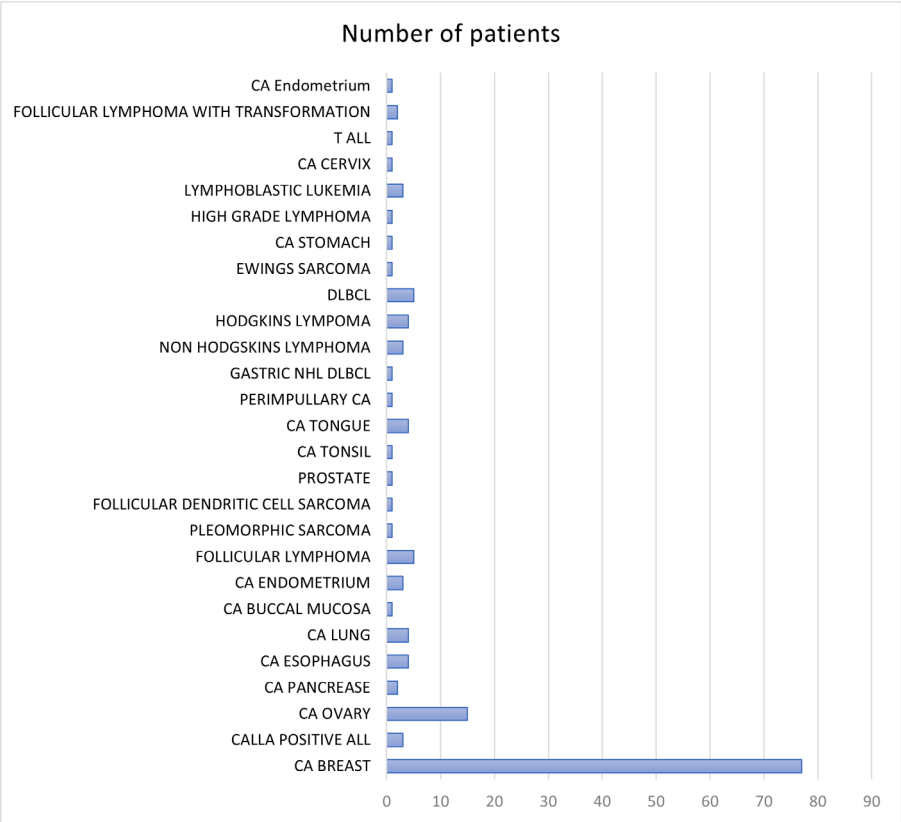


Figure 2.1: Patient Age Vs Total No of Patients.

Table 3: Adverse drug reactions reported with different anti-cancer drugs.

Regimen	Drugs used in combination	ADR reported (*N*=44)	Percentage
TAXOL	Pacalitaxel	2	4.54
carbotaxol	Pacalitaxel+Carboplatin	6	13.63
R-CHOP	Vincristine+Cyclophosphamide+Adriamycin+Rituximab	4	9.09
VDP	VINCRISTINE+DAUNOMYCIN+Prednisone	3	6.81
Oncovin	Vincristine	1	2.27
T-DM1, Taxol	PACALITAXEL + Ado-Trastuzumab Emtansine	4	9.09
Gemzar+DoceAqualip	Gemcitabine+Doceaqualip	2	4.54
carbotaxol+Herceptin	Pacalitaxel+Trastuzumab+Carboplatin	6	13.63
PACLIAQUALIP	Pacliaqualip	3	6.81
carbotaxol+zol	Paclitaxel+Carboplatin+Zoledronic Acid	5	11.36
NDLS+CP	Doceaqualip+Cyclophosphamide	2	4.54
TCH	Doceaqualip+Carboplatin+ Trastuzumab	6	13.63



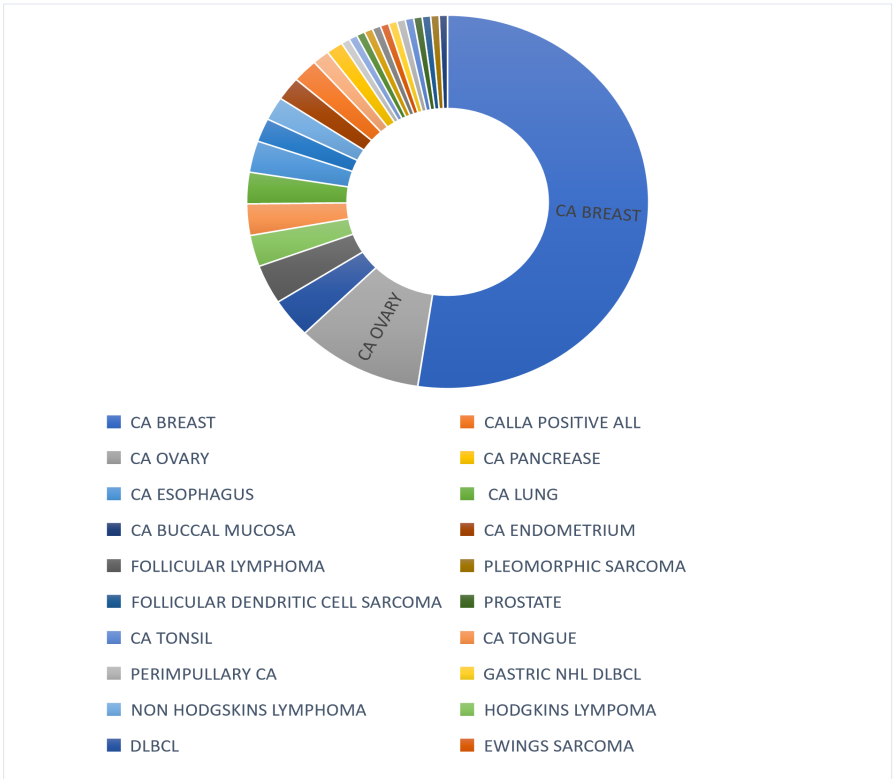


Figure 3: Represents the distribution pattern of different cancers within the study population.

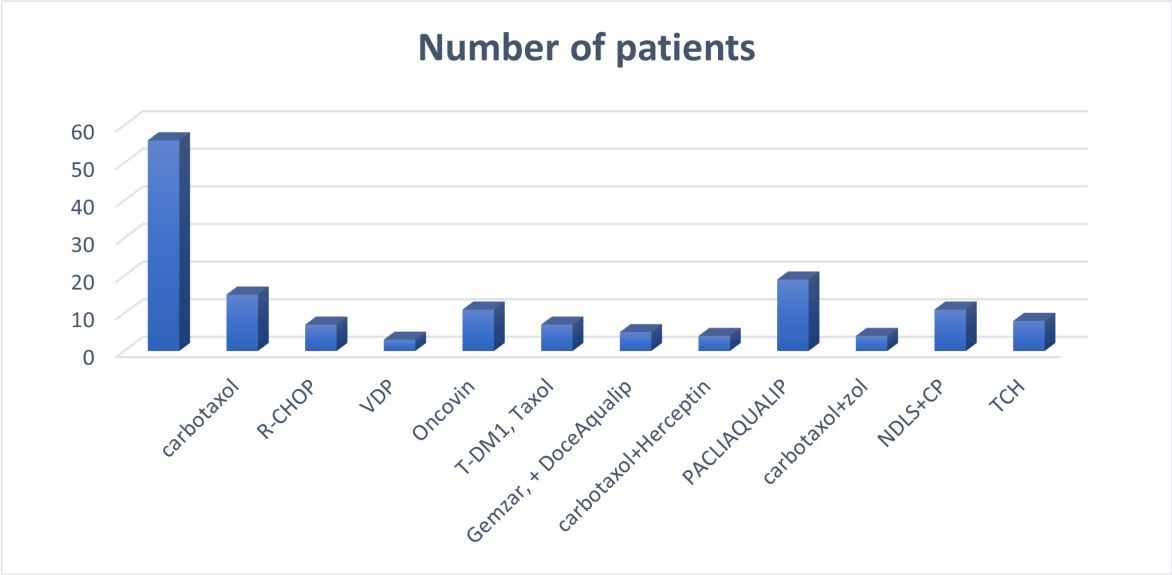


Figure 3.1: Anti-Cancer agents used in the study population.

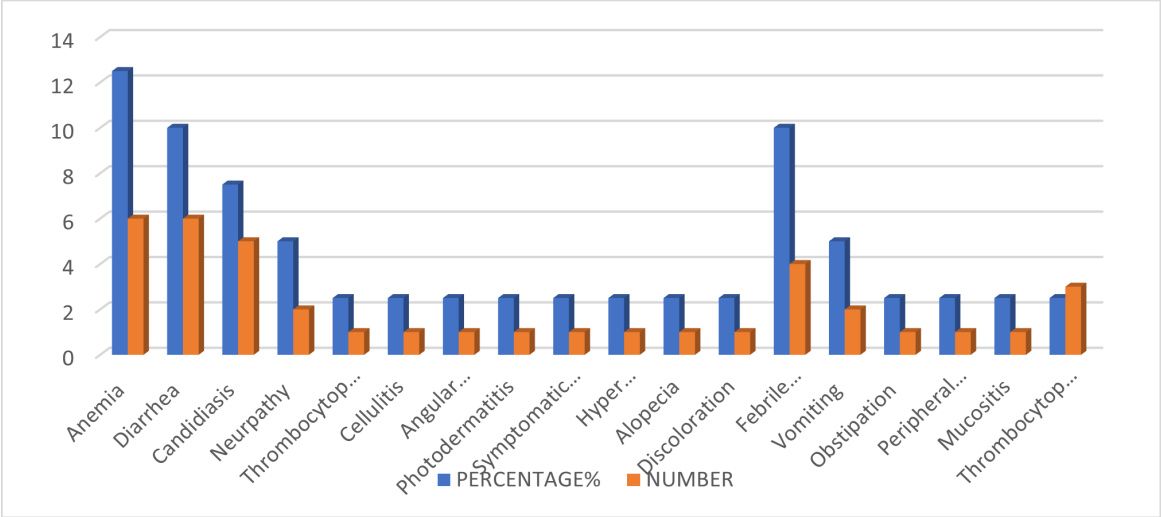


Figure 4: Anti-Cancer agents used in the study population.

enrolled in the study, 131 (87.33%) experienced ADRs. The decrease in the metabolizing capacity and excretory functions leads to accumulation of the drug in the body thereby increasing the risks of adverse effects were observed in the patients with the age group of 45-65 years. Breast cancer was noted to be in the maximum number of patients in this study (77.9%).

Figure 5 illustrates the observed adverse drug reactions for anti cancer agents used in patients.

Blood and gastrointestinal system were found to be reported with maximum number of adverse effects in the patients who were treated with combination of anti-cancer agents during this study. Anemia, febrile neutropenia were some notable adverse effects observed in the hematological system. Nausea (7.5%) and vomiting (5%) were the most common ADRs reported, followed by alopecia (2.5%), neutropenia (10%), and anemia (12.5%). Nausea and vomiting were reported by most of the patients and treated with doses of 5HT3 antagonists. The cancer chemotheraphy regimen includes medications filgrastim, tranexamic acid, antibiotics like ceftriaxone, ciprofloxacin, anti-histaminics, NSAIDs, multivitamins, anti-diarrhoeals, etc., for the management of adverse effects during treatment in the patients. When the patients were treated with platin derivatives, followed by antibiotics maximum number of adverse effects were reported (13.63%).

Table 4 shows Causality category-wise distribution of Adverse Drug Reactions (ADRs) identified at CyteCare tertiary hospital in India.

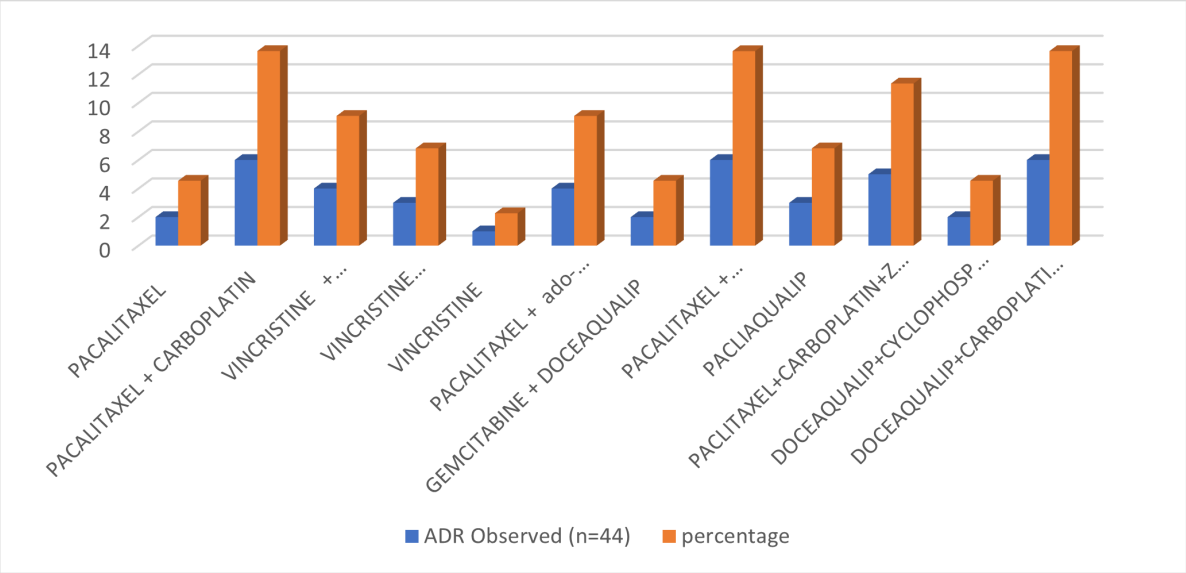


Figure 5: Observed adverse drug reaction for anti-Cancer agents used in the patients.

Table 4: Adverse drug reactions reported with different anti-cancer drugs.

WHO- UMC Causality assessment	
Categorization	**Total number of ADRS (*n*=44) %**
Certain	Nil
Probable	37(84.09)
Possible	8(18.18)
Unlikely/unclassified/unassessible	Nil
Severity assessment as per modified Hartwig and Siegel scale	
Mild	9(20.45)
Moderate	35(79.54)
Severe	1(2.27)
Preventability assessment as per Schumock and Thorton scale	
Not preventable	35(79.54)
Definitely preventable	3(6.81)
Probably preventable	6(13.63)

Based on the WHO-UMC criteria, the causality assessment of the ADRs in the study indicated that 37(84.09%) were probable and 8(18.18%) were possible. Rechallenge was not done in any of the patients, so no specific ADR was identified. The severity of the ADRs reported was evaluated according to the modified Hartwig and Siegel Scale, where the majority of the ADRs were moderate 35(79.54%), followed by mild in 9(20.45%) of the patients. Only 1(2.27%) of the ADRs were severe. Based on the modified Schumock and Thornton scale, maximum ADRs 35(79.54%) were not preventable, while 3(6.81%) were preventable, and 6(13.63%) were probably preventable.

LIMITATION

This study was conducted in CyteCare Hospital, Bangalore, but it had some limitations. The study was carried out in a short duration and was unicentric in nature. Additionally, very few number of ADRs analysed. It was difficult to corelate any specific adverse drug reaction to a specific drug, as all the patients who were included in the study were treated with multiple drug regimen.

CONCLUSION

The investigation and evaluation of adverse effects of chemotherapy agents for causality, degree of severity, and preventability has highlighted the crucial role played by

Pharmacovigilance in cancer chemotherapy. Due to the complex nature of chemotherapy regimens, the incidence of adverse drug reactions is quite high. Sadly, many ADRs go misdiagnosed and underreported, which is why Pharmacovigilance is crucial in the oncology department for ensuring the safety and efficacy of the medications. Regular monitoring, coupled with careful reporting, can help reduce the incidence of adverse effects, increase patient compliance, and cut down on the morbidity, mortality, and financial burden of the treatment for patients. Creating awareness among treating physicians and providing adequate training for healthcare personnel can significantly aid in the diagnosis at the earliest stage and prompt management of adverse effects.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ADR: Adverse drug reaction; **Her2:** Human epidermal growth factor receptor 2; **MTDD:** Microtubule damaging drug; **PV:** Pharmacovigilance; **WHO-UMC:** World Health Organisation and Uppsala Monitoring Centre.

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