INTERNATIONAL JOURNAL
OF
PHARMACEUTICAL SCIENCES
AND
RESEARCH

PRESCRIPTION ANALYSIS AND MONITORING OF ADVERSE DRUG REACTIONS OF ANTICANCER AGENTS IN TERTIARY CARE HOSPITAL

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ABSTRACT: Objective: Cancer being a global threat and deadly disease, necessitate the use of anticancer agents. Hence, continuous drug utilization evaluation studies and Adverse Drug Reaction (ADR) reporting should be carried out in the oncology departments of health care systems. The objective of the study was to identify various types of cancer, assess commonly prescribed anticancer agents using WHO prescribing indicators and report ADRs associated with the anticancer treatment. **Materials and Methods:** An ambispective observational study was conducted for a period of 6 months in the oncology daycare and in-patient department. All patients receiving at least a single anticancer agent of all age groups of either sex were included in the study. Data was collected in a self-designed patient profile form from the medical records department. Information on drug utilization patterns and ADRs were studied. **Results:** Breast cancer was the most prevalent cancer observed with more preponderance in females. Paclitaxel was the most commonly used anticancer agent, followed by carboplatin and cisplatin. Granisetron was the widely used adjuvant drug. Only 57.86% of drugs were taken from the essential drug list (EDL), which was suboptimal compared to other drug utilization studies. Only 16% of patients developed ADRs. Anemia and weakness were the most commonly reported ADRs. **Conclusion:** Only 57.86% of drugs were prescribed from the essential drug list. ADRs caused by anticancer agents can be reduced with rational and judicious preventive measures.

INTRODUCTION: Cancer is a group of diseases that is characterized by uncontrolled cell growth and spread to other parts of the body [1, 2]. A benign tumor can grow but does not spread into or invade nearby tissues. A cancerous tumor is malignant, meaning it can grow and spread into nearby tissues and travel to distant parts of the body.

Many cancers form solid tumors, but hematologic cancers like leukemia, lymphoma and myeloma, generally do not [2, 3, 4]. Worldwide, about 19.3 million new cases were diagnosed, and 10 million people succumbed to cancer in 2020. It is expected to rise to 19 million by 2025.

In India, 1.1 million new cases are diagnosed, and more than 0.6 million people die each year because of cancer [1, 5, 6]. According to the National Cancer Registry Programme (NCRP) report, in India, 1.39 million new cases were diagnosed in 2020, and it is likely to rise to 1.57 million by 2025 [5, 6]. Management options for cancer include surgery,

radiation therapy, chemotherapy, hormonal therapy, immunotherapy, targeted therapy, and clinical trials [1, 5]. First-line recommendation for anticancer therapy depends upon the cancer type and stage at the time of diagnosis. Chemotherapy alone or as a component of the multimodality approach remains integral to cancer management. Anticancer drugs with personalized dosing regimens are used to overcome cancer cell heterogeneity and kill drug-resistant cancer cells [4, 7, 8, 9]. Extensive research shows that most cancers are detected in their later stages when it has compromised the function of one or more vital organ systems. Thus, this deadly disease necessitates using anticancer agents in multiple cycles along with adjuvant drugs, which leads to polypharmacy, increasing the economic burden [10].

Patients undergoing treatment are at increased risk of ADR, which gradually aggravates their quality of life. Complications, secondary to anticancer treatment, increase morbidity and mortality. Multiple cycles of anticancer regimen may result in ADR, which requires monitoring. Significant variations in the response rate of individual anticancer drugs and intolerability of combination regimens are common problems with cancer treatment [5, 11, 12, 13]. This necessitates careful observation and evaluation of cancer therapy to monitor ADR and optimize anticancer therapy with minimal toxicity and improved efficacy [8, 13]. Drug utilization evaluation (DUE) studies aim to evaluate factors such as prescribing, dispensing, medication administration, and its associated events. DUE of anticancer drugs becomes necessary as their irrational use has generated a significant health problem in the current medical practice. This indicates a need to promote DUE research, which is an effective tool to rationalize the use of drugs in the population [5, 14, 15]. The present study emphasizes the prescription pattern of anticancer agents and the assessment of ADR.

MATERIALS AND METHOD: An ambispective, observational study was conducted in the oncology department of Aditya Birla Memorial Hospital, Chinchwad. It was carried out for a period of six months, from February 2021 to July 2021. Before the initiation of the study, ethical approval was obtained from the Ethics Committee of Aditya Birla Memorial Hospital, Chinchwad

(ABMH/Academics/EC/3607). The sample size was calculated based on the average number of in-patients admitted and registered in the earlier six months of the study period. A total of 163 patients were recruited for the study from February 2021 to July 2021. Patients of all ages and gender receiving at least a single anticancer agent were included in the study. Pregnant women and patients with insufficient data and records were excluded from the study. Informed consent was obtained from those enrolled in the prospective study. Data were collected from the electronic Medical Records Department (MRD) using RHIS software. Prescription parameters needed for the study were recorded in a specially designed Cancer Patient Profile Form (Annexure III), and adverse drug reactions were documented in the Central Drugs Standard Control Organization (CDSCO) ADR reporting form. Results were calculated in terms of number and percentage using Microsoft Excel 2019.

RESULTS: The majority of patients, 81 (49.69%) were in the age group of 41-60 years, followed by 58 patients (35.58%) in >60 years, 22 patients (13.49%) in 19-40 years, 2 patients (1.22%) in 0-18 years of age group. The mean age of participants was found to be 40.75 years.

TABLE 1: AGE RANGE (IN YEARS) AND CORRESPONDING PERCENTAGE

Age Range	Number of Patients (N=163)	Percentage (%)
0-18	2	1.22%
19-40	22	13.49%
41-60	81	49.69%
>60	58	35.58%
Mean Age	40.75	
SD	±13.3	

The study revealed that out of 163 patients, 65 were male, and 98 were female, as shown in **Fig. 1.**
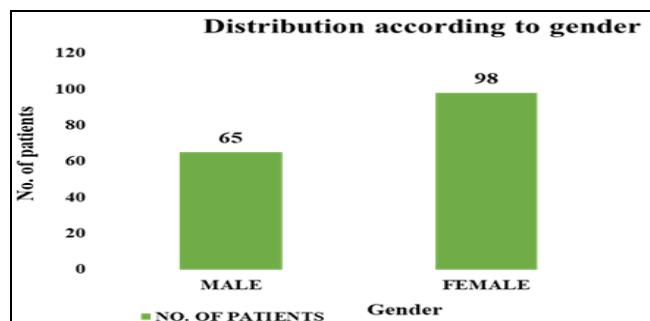

FIG. 1: DISTRIBUTION OF PATIENTS ACCORDING TO GENDER

Types of Cancer: During the study, a total of 32 different types of cancer were observed. Breast cancer was the most prevalent of all cancers, constituting about 24.53% of the total study population.

The next prevalent cancers were ovarian cancer (9.81%) followed by lung cancer (9.20%). In female patients, breast cancer was most prevalent, followed by ovarian and uterine cancer. In male patients, lung cancer was most prevalent.

This was followed by cancer of the oral cavity and stomach cancer. The most common types of cancers in males and females are shown in **Table 3,** and their graphical representation is shown in **Fig. 2.**

TABLE 2: DIFFERENT TYPES OF CANCER IN THE STUDY POPULATION

Type of Cancer	No. of Patients (N=163)	Percent of Patients (%)
Breast	40	24.53%
Ovary	16	9.81%
Lung	15	9.20%
Cervix	13	7.90%
Oral cavity	9	5.52%
Hodgkin's lymphoma	8	4.90%
Colon	7	4.29%
Stomach	7	4.29%
Esophagus	6	3.68%
Prostate	5	3.06%
Rectal	4	2.45%
Oropharynx	3	1.84%
Bone and articular cartilage	3	1.84%
Multiple myeloma	3	1.84%

TABLE 3: DISTRIBUTION OF CANCERS IN MALE AND FEMALE PATIENTS

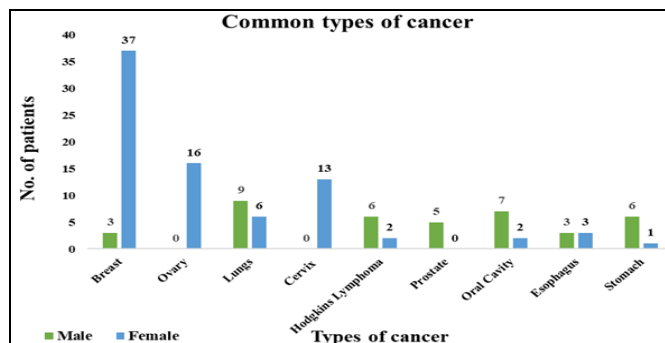| Cancer	Breast	Ovary	Lungs	Cervix	Hodgkins Lymphoma	Prostate	Oral Cavity	Esophagus	Stomach
Male	3	0	9	0	6	5	7	3	6
Female	37	16	6	13	2	0	2	3	1

FIG. 2: DISTRIBUTION OF CANCER IN MALE AND FEMALE PATIENTS

System-wise Distribution of Cancers: Cancers of reproductive organs (42.94%) followed by gastrointestinal cancer (14.72%), head and neck cancer (14.11%), and respiratory cancer (9.20%) were more predominant among the study population.
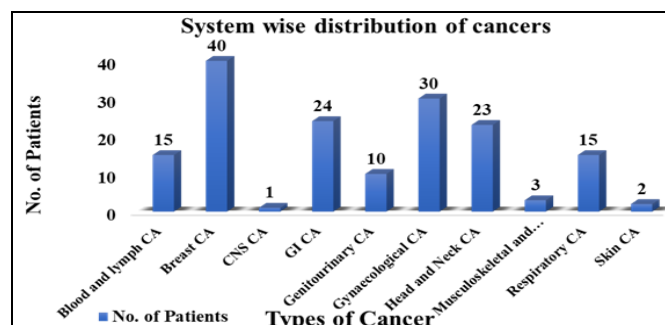

FIG. 3: GRAPHICAL REPRESENTATION OF DIFFERENT TYPES OF CANCERS

WHO Core Drug Indicators for Anticancer agents: The WHO core drug use indicators were also evaluated in this study. The prescribing indicators and health facility indicators were studied, and their results are depicted in **Table 4,** the percentage of anticancer drugs prescribed by generic names was 92.87%. The percentage of anticancer drugs prescribed in injection form was 98.81%. 57.14% of anticancer drugs are prescribed from the essential drugs list.

TABLE 4: COMPARISON OF WHO CORE DRUG INDICATORS

WHO Core Drug Indicators		
A. Prescribing Indicators		
Serial No.	Prescribing Indicators	Value
1	The average number of anticancer drugs per prescription	2.067
2	Percentage of anticancer drugs prescribed by generic name (%)	92.87%
3	Percentage of anticancer drugs prescribed in an injection form (%)	98.81%
4	Percentage of anticancer drugs prescribed from the essential drugs list (%)	57.14%
B. Health Facility Indicators		
Serial No.	Health Facility Indicators	Value
1	Availability of copy of essential drugs list	No

Anticancer Prescriptions:

Regimens Commonly Prescribed: In the study population total of 181 anticancer prescriptions were observed. The anticancer prescription consists of anticancer agents and adjuvant medications. In total, 67 anticancer regimens were recorded. The different regimens and their corresponding number of prescriptions are shown in **Fig. 4.**
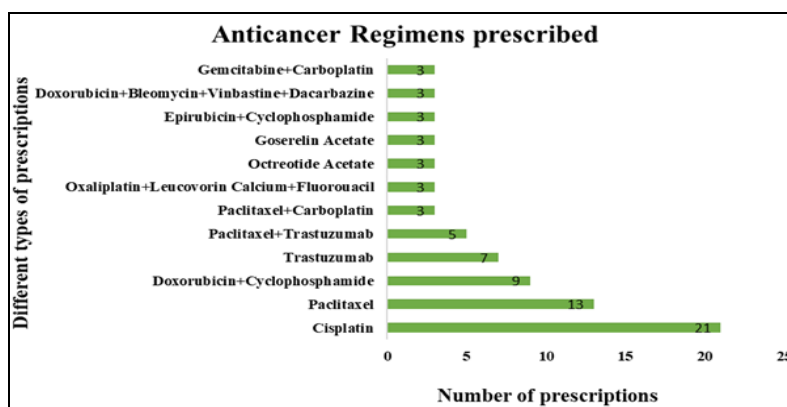

FIG. 4: COMMONLY PRESCRIBED ANTICANCER REGIMENS

Anticancer Regimens in Common Cancer: The prescribed anticancer regimens in various types of cancers are explained in **Table 5**. In breast cancer patients, Paclitaxel alone was found to be commonly used. Paclitaxel + Carboplatin was the most commonly prescribed regimen for ovarian cancer as well as lung cancer, while cisplatin was the most common regimen used in cervix cancer patients.

TABLE 5: COMMONLY PRESCRIBED REGIMENS CORRESPONDING TO VARIOUS CANCERS

Common Type of Cancer	Commonly Used Regimen	No. of Patients
Breast Cancer	Paclitaxel	12
	Doxorubicin + Cyclophosphamide	8
	Trastuzumab	7
	Paclitaxel +Trastuzumab	5
	Epirubicin + Cyclophosphamide	3
Ovarian Cancer	Paclitaxel + Carboplatin	10
	Carboplatin + Doxorubicin + Bevacizumab	2
	Paclitaxel	2
Lung Cancer	Paclitaxel + Carboplatin	6
	Gemcitabine + Vinorelbine	3
	Pemetrexed + Carboplatin + Bevacizumab	1
Cervix Uteri Cancer	Cisplatin	6
	Paclitaxel + Carboplatin	3
	Bevacizumab + Paclitaxel + Carboplatin	1

Commonly Used Class of Anticancer Agents: The commonly used class of anticancer agents was alkylating agents, followed by antimetabolites, plant alkaloids & monoclonal antibodies. In alkylating agents, Carboplatin was a commonly prescribed drug **Fig. 5.**

TABLE 6: COMMONLY USED CLASSES OF ANTICANCER AGENTS

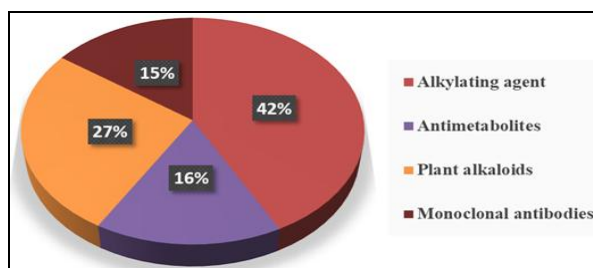| Drug class	Commonly used class of Anticancer agent
Alkylating agent	110
Antimetabolites	42
Plant alkaloids	69
Monoclonal antibodies	39

FIG. 5: COMMONLY USED CLASS OF ANTICANCER AGENT

Adjuvant Medications Along with Anticancer agents: Adjuvant drugs include medications that reduce the side effects of anticancer agents. The list of adjuvant drugs and their corresponding number of prescriptions is shown in **Table 7.**

TABLE 7: LIST OF ADJUVANT DRUGS

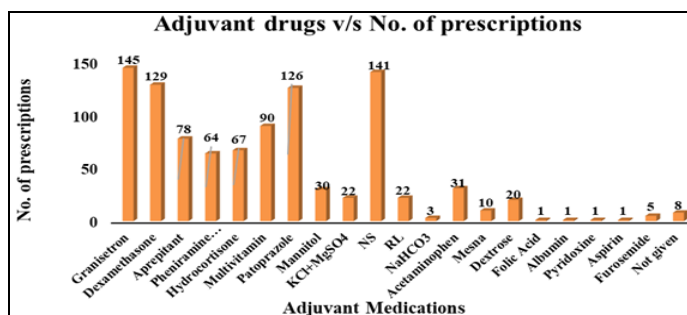| Adjuvant Drugs	No. of Prescriptions (N=181)
Granisetron	145
NS	141
Dexamethasone	129
Pantoprazole	126
Multivitamin	90
Aprepitant	78
Hydrocortisone	67
Pheniramine maleate	64
Acetaminophen	31
Mannitol	30
KCl+MgSO$_4$	22
Ringer Lactate	22
Dextrose	20
Mesna	10
NaHCO$_3$	3
Folic Acid	1
Albumin	1
Pyridoxine	1
Aspirin	1
Furosemide	5
Not given	8

FIG. 6: ADJUVANT DRUGS V/S NO. OF PRESCRIPTIONS

Adverse Drug Reactions of Anticancer Drugs:

Incidence of ADR: ADRs were observed in only 26(15.92%) patients, and 137(84.04%) did not have any ADR.
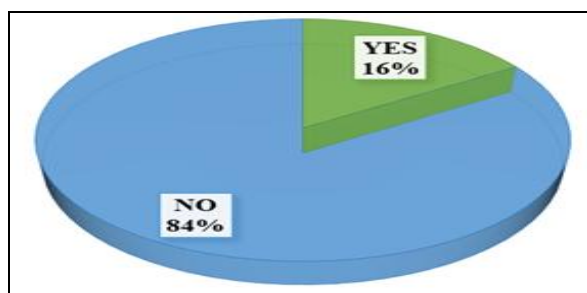
FIG. 7: INCIDENCE OF AN ADR

ADR with a Suspected Regimen: Anemia was the most common ADR (8) for Cisplatin, Gemcitabine + Carboplatin, Pemetrexed + Carboplatin, R-CHOP, R-EPOCH, Bevacizumab + Topotecan, P+C, Carfilzomib+ Lenalidomide regimens. The next most common ADR was weakness (8) for Cisplatin, P+C, Gemcitabine + Carboplatin, Carfilzomib + Lenalidomide, Gemcitabine, R-CHOP, R-EPOCH, Cisplatin + MTX + 5FU + Nivolumab regimens. The complete list of ADRs and their incidences corresponding to various anticancer regimens are listed in **Table 8.**

TABLE 8: INCIDENCE OF ADR IN DIFFERENT TYPES OF ANTICANCER REGIMENS

ADR	n (Incidence of ADR)	REGIMEN
Anemia	8	Cisplatin, Gemcitabine + Carboplatin, Pemetrexed + Carboplatin, R-CHOP, R-EPOCH, Bevacizumab + Topotecan, P+C, Carfilzomib+ Lenalidomide
Weakness	8	Cisplatin, P+C, Gemcitabine + Carboplatin, Carfilzomib + Lenalidomide, Gemcitabine, R-CHOP, R-EPOCH, Cisplatin + MTX + 5FU + Nivolumab
Anorexia	6	Cisplatin, R-CHOP, P+C, C+MTX+5FU+Nivolumab, Trastuzumab + Venorelbine + Zoledronic Acid, Gemcitabine
Constipation	4	R-EPOCH, Bevacizumab + Topotecan, Doxorubicin + Cyclophosphamide + Paclitaxel, Trastuzumab + Venorelbine +Zoledronic Acid
Abdominal Pain	3	P+C, Trastuzumab + Venorelbine + Zoledronic Acid, Bevacizumab + Topotecan
Oral Ulcers	3	Cisplatin, Gemcitabine + Carboplatin, MTX + 5FU + Oxaliplatin
Diarrhea	3	P+C, Oxaliplatin + Leucovorin + 5FU, R-EPOCH
Abdominal Distension	2	P + C, Atezolizumab
Fever	2	Gemcitabine + Carboplatin, Cisplatin + Etoposide
Vomiting	2	MTX + 5FU + Oxaliplatin, Gemcitabine
Breathlessness	2	Gemcitabine + Carboplatin, R-EPOCH
Pedal Edema	2	Gemcitabine, Atezolizumab
Dyspnoea on Exertion	1	P+C
Hypersensitivity to carboplatin	1	Carboplatin + Paclitaxel + Cetuximab
Chest Pain	1	Gemcitabine + Carboplatin
Thrombocytopenia	1	Gemcitabine + Carboplatin
Nausea	1	MTX+5FU+Oxaliplatin
Dysphagia	1	Cisplatin
Burning Micturation	1	Carfilzomib + Lenalidomide
Red spots on the body	1	Carfilzomib + Lenalidomide
Cough	1	R-CHOP
Vertigo	1	Gemcitabine
Arthralgia	1	Gemcitabine + Cisplatin/Pembrolizumab
Hypoglycemia	1	P+C
Giddiness	1	P+C
Drowsiness	1	P+C
Urine Retention	1	Atezolizumab
ACS	1	Gemcitabine + Vinorelbine

DISCUSSION: Among 163 study participants, the age group 41-60 years (n=81) was mostly affected by cancer, followed by >60 years (n=58). The accumulation of age-related changes in a biochemical process that helps control genes may be associated with an increased risk of cancer in older people. Because of rising in the number of chronic proliferation of loci, deteriorating immune surveillance, and hormonal changes, aging renders an organism susceptible to cancer. A Greater prevalence of cancer in females than in males was observed; similar was reported by Sandeep K. *et al.* [11, 14, 16].

Cancers were distributed as per body system affected, and it was found to be affecting every body system, revealing the non-specific nature of the disease. In this study, breast cancer was most predominant followed by cancer of the ovary, lung, cervix uteri, and oral cavity. This assertion is congruent with a survey conducted by Sunny S. *et al.,* and Manichavasagam M. *et al.* [14,17] Increased risk of breast cancer is associated with family history, obesity, physical inactivity, consumption of processed foods, delayed childbearing, fewer children, early age at menarche and shorter duration of breastfeeding. Most females have breast and ovarian cancers due to female sex hormone receptors [18, 19]. In males, lung cancer was the most prevalent, followed by oral cavity and stomach cancer. Surveys by Kamlekar *et al.* and Spandana S. *et al.* in different states of India and Manichavasagam M. *et al*. also reported a similar observation. Smoking and the use of tobacco products are the main causes of lung cancers [11, 14, 20]. Although other factors such as radon gas, asbestos, air pollution exposure, and chronic infections also contribute to this [21].

Paclitaxel was the most commonly prescribed drug in our setting, followed by platinum compounds, carboplatin & cisplatin. The results of Aggarwal M *et al.* and Mugada V *et al.* studies show that cisplatin was the most prescribed drug, followed by 5-FU, carboplatin & paclitaxel, which does not agree with the pattern of our results [1, 16]. The difference in drug utilization between studies may be attributed to the cancer diagnosis & stage, management guidelines, and patient status. Our study reveals that the most common class of anticancer agents used were alkylating agents (35.9%) followed by taxanes (18.30%), antimetabolites (13.7%) and monoclonal antibodies (12.7%). The present study findings are similar to the study done by Bepari A *et al.* [5] In breast cancer the most frequently used regimen was paclitaxel followed by doxorubicin + cyclophosphamide, trastuzumab. This finding was similar to the study done by Bepari A. *et al*. In lung cancers, the anticancer regimen of paclitaxel + carboplatin, gemcitabine has been used in our study population, which proves to be similar to other studies [5, 21].

Anticancer drugs are used along with adjuvant & supplementing medicines to reduce the side effects. Nausea and vomiting can be prevented in almost 70%-80% of patients, with the correct use of antiemetics [16]. Granisetron, dexamethasone, pantoprazole, and aprepitant were the most common drugs for chemotherapy-induced nausea-vomiting and to prevent gastric acid reflux diseases [22]. Besides these, adjuvant drugs forced hydration in the form of NS before, on the day of chemotherapy, and following cisplatin with furosemide was also given to prevent nephrotoxicity. Mannitol is also given along with furosemide as palliative therapy. An anticancer regimen containing cisplatin and carboplatin usually causes hypomagnesemia and hypokalemia. As a result, almost all patients receiving cisplatin or carboplatin-based chemotherapy regimen were given potassium chloride and magnesium sulfate. It has been discovered that when prophylactic magnesium supplements are given, it reduces cisplatin-induced renal damage without interfering with the drug's anticancer effect. Similar reports are documented by studies conducted by Jack C *et al.,* Mugada V *et al.,* and Janowitz T *et al.* [16, 22, 23].

Furosemide was always co-prescribed with $MgSO_4$ to reduce cisplatin nephrotoxicity. Pheniramine maleate was used among 80 patients receiving paclitaxel anticancer drugs to prevent paclitaxel-induced allergic reactions. Mesna was used along with cyclophosphamide drug to prevent the occurrence of hemorrhagic cystitis. A similar was observed in studies conducted by Harada T. *et al.,* Mugada V. *et al.,* and Jimoh A. *et al.* [16, 24, 25]. The prescribing indicators signify that the average number of anticancer drugs per prescription was 2.067, which is comparatively lower than that of similar studies conducted in Brazil (2.4), Jordan

(2.3) and other places in India (2.7) [11, 16, 26]. The occurrence of encounters with injectables was 98.81%, far off WHOs prescribed (13.4-24.1%), and this significant shift is seen may be because most anticancer agents are injectables. Even though injectable preparations are inconvenient, expensive, require expertise, introduce infection, and can cause various toxicity issues in cancer patients, their use is preferred because of large and rapid dose delivery, desired plasma concentration can be attained to minimize side effects, versatility and flexibility in personalized drug dosing can be achieved [11, 16, 26].

About 92.87% of drugs in this study were prescribed by generic name, which was significantly better than 77% recorded in an earlier study conducted in the other parts of the country by Bepari et al. and Mugada V. et al. which was 93% [5, 16]. The percentage of anticancer drugs prescribed from the essential drug list was 57.14%, suboptimal compared to other studies conducted by Mathew M et al. (78.92%), Mugada et al. (88.4%) and Aggarwal M. et al. (93%). The drugs are prescribed based on the hospital formulary [1, 9, 16].

Anticancer therapy is routinely prescribed to more than 50% of cancer patients, but their contribution to overall cure is only 2%-5%. ADRs are considered an unavoidable component of anticancer therapy and are accepted by patients and healthcare providers [16]. Even though safe & truly curative anticancer agents are few, they are being used widely as they have contributed to improvements in overall survival and quality of life of cancer patients. Anticancer agents are associated with severe side effects and increased patient economic burden. Many new anticancer agents are being developed continuously but ADR incidence is also increasing simultaneously. Different anticancer regimens contribute further to ADRs, many of which can be prevented by anticipatory prophylactic use of drugs [25]. In this study, out of 163, only 16% of patients developed ADR and this was not in accordance with other similar studies done before. The majority of patients were females-14(53.84%), which is consistent with findings of a previous study done by Jimoh A. et al., and 12(46.15%) were males who developed ADR. It is a well-known fact that women are 50%-75% more likely than men to experience an ADR, probably

due to increased bioavailability of drugs, lower organ sizes, lower body weight, higher % of body fat, lower volume of distribution, and greater awareness in females than in males [25, 26]. The most prevalent ADR encountered in the present study involves anemia (30.76%), weakness (30.76%), anorexia (23.07%), constipation (15.38%) and abdominal pain, oral ulcers, diarrhea (11.53% each). This result pattern was similar to the study conducted by Jimoh A. O. et al. anemia was most common in our setting which was consistent with findings of studies done by Ramasubbu SK et al. Anemia was treated with transfusion in most of the patients.

The most commonly prescribed regimen in these patients was paclitaxel + carboplatin and gemcitabine followed by cisplatin which was found similar to the study done by Kamlekar et. al. [11, 25, 27]. Because only documented ADRs were included in the study, exact dates, nature, intensity, frequency, and time of occurrence were not known; thus causality assessment could not be ascertained. All the observations and results were mainly based on the patient complaints which were documented, and very few laboratory investigations reports. Due to the COVID pandemic, considering patients immunocompromised status only documented ADRs which were reported at the time of the cancer treatment cycle were included in the study. A previous study reports that about 95% of reactions are predictable, and only 56% of them can be prevented. Our study population had a lower incidence of ADRs, which could be attributed to prompt premedications and undocumented ADRs. An encouraging fact was dedicating preventive measures in place may have helped to prevent and control ADRs. This stresses the importance of establishing a huge scope for research and betterment in this area [13, 16, 26, 27].

CONCLUSION: From the present study, we can conclude that the prevalence of cancer increases with an increase in age. The prevalence of cancer is more in females as compared to males. Breast and ovarian cancer were the most common cancers observed, with more preponderance among females. Paclitaxel was the most commonly used anticancer agent, followed by alkylating agents - carboplatin and cisplatin. The most commonly used adjuvant drugs in our study include granisetron

followed by NS, dexamethasone and aprepitant. According to this study, a higher number of injectables and fewer drugs are prescribed from the essential drug list than indicated by WHO prescribing indicators. The higher number of injectables and fewer drugs prescribed from EDL could be due to the unavailability of anticancer agents in other dosage forms and the use of newer anticancer agents that were not included in the EDL. The most commonly reported ADRs were anemia, weakness, abdominal pain, and constipation. Anticancer agents are known to cause ADRs. However, it can be reduced with rational and judicious preventive measures. ADR documentation and reporting should be encouraged.

CONFLICTS OF INTEREST: There are no conflicts of interest.

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