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Adverse Drug Reactions to Cancer Chemotherapy: The role of Clinical pharmacist in Onco-pharmacovigilance

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Abstract:
BACKGROUND: *Cancer is the uncontrolled growth and spread of cells. The global cancer burden is estimated to have risen to 18.1 million new cases and 9.6 million deaths in 2018. One in 5 men and one in 6 women worldwide develop cancer during their lifetime, and one in 8 men and one in 11 women die from the disease. All the different types of cancers can be prevented by avoiding exposure to common risk factors. In addition, a significant proportion of cancers can be cured, by surgery, radiotherapy or chemotherapy, especially if they are detected early.*
AIM: *To Identify, Analyze and Report the Adverse drug reactions that occurs due to Chemotherapy and targeted agents.*
METHOD: *This is a Prospective Observational study which was carried out in and around Guntur over a period of 6 months i.e. June 2019 to November 2019. About 150 study participants were analyzed for demographic profile, Organ-system wise distribution of ADR's, Common and rare ADR's encountered, Grade-wise severity assessment of ADR's and to determine incidence and prevalence of different types of Cancer in different age groups, Genders, a sample size of 1000 subjects were included.*
RESULTS: *A total of 948 Chemotherapy-induced ADR's were detected with different grades from a total of 150 patients during the study period. The common drugs involved in causing ADR's were Microtubule damaging agents, Platinum compounds, Anti-metabolites. Hematological system (91.3%; n=137) was the most frequently involved organ system with Anemia, Thrombocytopenia being most common manifestations. According to the severity assessment scale (CTCAE 4.0) it was found that most of the reactions were of Grade-I (Mild, 51.5%) followed by Grade-II (Moderate, 44.6%) and very few people were found with Grade-III (Severe, 3.7%) and Grade-IV (Life threatening, 0.2%). The Epidemiological results of this study revealed that there was a higher incidence of different types of Cancers among people with age of 51-60 years and females were highly affected when compared to males.*
CONCLUSION: *ADR's pose additional worse outcomes in patients treated with Chemotherapy since they have a negative impact on the patient's QOL and in addition escalates cost of therapy. So, to ensure the preventability of ADR's in many cases, timely reporting of ADR's and effective ADR monitoring system (Onco - pharmacovigilance) could be the need of hour with the involvement of Oncologists, Radiotherapists and Onco - surgeons*

Keywords: *Chemotherapy, Adverse drug reactions, Onco-pharmacovigilance, CTCAE, Severity*

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I. Introduction

Cancer is the uncontrolled growth and spread of cells which often invades surrounding tissue and can metastasize to distant sites. Global cancer burden is estimated to have risen to 18.1 million new cases and 9.6 million deaths in 2018. Cancers of the lung, female breast, and colorectum are the top three cancer types in terms of incidence, and are ranked within the top five in terms of mortality. Risk factors for these different types of cancers include Tobacco use, Alcohol use, Dietary factors, Overweight and obesity, Physical inactivity, Chronic infections, Environmental and occupational risks. Not only the lifestyle modifications, early screening & early diagnosis plays a major role to prevent the progression of the cancers, as there is no single test that can accurately diagnose cancer, the complete evaluation of a patient usually requires a thorough history and physical examination along with diagnostic testing. A significant proportion of cancers can be cured by surgery, radiotherapy, chemotherapy, Immunotherapy, Targeted therapy, hormonal therapy, stem cell transplantation, especially if they are detected early. Chemotherapy, a multimodal approach to oncological treatment, involves highly complex regimens and hence accounts to high susceptibility toward adverse drug reactions (ADRs). Recent study shows that incidence of ADR's ranging from as low as 0.15% to as high as 30%. Most of the ADR's with these drugs are unreported due to unawareness of healthcare professionals, lack of time to report

and a dearth of sufficient staff in the hospitals which may be the predominant factors behind the increased economic burden to the patient due to increased length of hospital stay, increased health cost. Hence it is necessary to recognize the pattern of ADRs occurring with anticancer drugs so as to enhance the quality of life and to minimize the cost of ADR related hospitalization among cancer patients.

II. Material And Methods

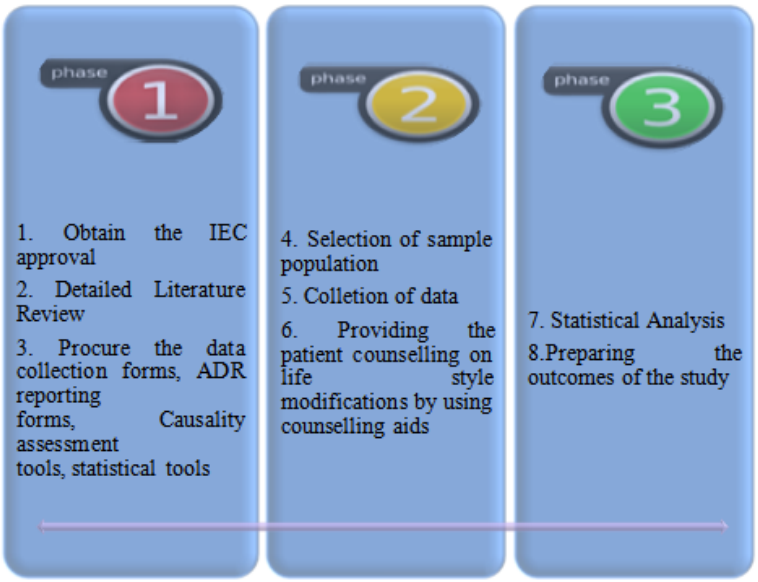
STUDY DESIGN:
A Prospective Cross-sectional Study
STUDY PERIOD:
This study was conducted for a period of six months i.e. from June to November 2019.
STUDY SITE:
Cancer hospitals located in and around Guntur
SAMPLE SIZE CALCULATION:
The sample size was estimated on the basis of a single proportion design. The target population from which we randomly selected our sample was considered 1000. We assumed that the confidence interval of 10% and confidence level of 95%. The sample size actually obtained for this study was 150 patients.

MATERIALS:
- Informed consent document
- Data collection form
- Counselling aids- Patient information leaflets
- Causality assessment scale- CTC version 4.0
- ADR Reporting form

STUDY CRITERIA:
INCLUSION CRITERIA:
1. Patients who developed atleast one ADR due to Anti-cancer drugs.
2. Patients with other co-morbidities were included in the study.
3. Patients with all age groups who developed ADR's due to cancer chemotherapy drugs.

EXCLUSION CRITERIA:
1. Patients who are receiving radiotherapy concomitantly with chemotherapy agents.
2. Patients who are on combinational therapy with Chemotherapy and targeted agents.
3. Patients who are experiencing adverse effects due to administration errors, non- compliance or overdose of drugs were excluded from our study.
4. Patients who are not willing to participate in the study were excluded.

PLAN OF WORK:



STUDY METHOD:

- Study is conducted in and around Guntur.
- A data collection form will be developed in which all the details of the patients are noted.
- Consent form will be taken from subjects who wish to participate in our study.
- Patients will be given adequate knowledge on cancer- its early screening measures and also on Dietary changes, lifestyle modifications have to be followed.
- Subjects who are not willing to participate in the study will also be counseled with the help of information leaflets.
- After collection of data from the patients who had developed atleast one type of ADR due to cancer chemotherapy will be assessed by using CTCAE version 4.0 assessment scale and the patients were informed about their severity of disease, ADRs.
- Patients who understood that they were at severe stage of disease or with severe ADR's were advised for to attend for regular follow-up and counseled about the importance of medication adherence, ADR's severity & life style modifications which helps to reduce hospitalization.
- The data will be analyzed by using descriptive analysis, CTCAE scale, and suitable statistical tests.

STATISTICAL ANALYSIS

Student's *t*-test was used to ascertain the significance of differences between mean values of two continuous variable. The level $P < 0.05$ was considered as the cutoff value or significance.

III. Results

FREQUENCY DISTRIBUTION OF DIFFERENT TYPES OF CANCERS

This study was conducted over a period of 6 months in a total of 1000 sample population.

TABLE 1: INCIDENCE OF DIFFERENT TYPES OF CANCERS

S.NO	TYPES OF CANCER	NO. OF CASES (n)	FREQUENCY (%)
1.	Breast cancer	182	18.2 (F -18, M - 2)
2.	Cervical cancer	172	17.2 (F- 17, M - 2)
3.	Ovarian cancer	86	8.6
4.	Stomach cancer	69	6.9 (F-2, M - 4.9)
5.	Lung cancer	65	6.5 (F-2.3, M - 4.2)
6.	Tongue cancer	36	3.6 (F- 1.3, M-2.3)
7.	Neck cancer	28	2.8 (M)
8.	Vault cancer	28	2.8
9.	HCC	28	2.8 (F-1.1, M-1.7)
10.	Colon cancer	27	2.7(F-1.1, M-1.6)
11.	Renal cell ca	22	2.2 (F-0.1, M-2.1)
12.	Rectal cancer	21	2.1 (F-0.1, M-2.0)
13.	Hodgkin's lymphoma	20	2.0 (F-0.2, M-1.8)
14.	Buccal mucosa cancer	20	2.0 (F-0.5, M-1.5)
15.	Gall bladder cancer	16	1.6 (F-0.1, M-1.5)
16.	Penis cancer	16	1.6
17.	Prostate cancer	16	1.6
18.	Cervix cancer	15	1.5 (F)
19.	CLL	14	1.4 (F-0.8, M-0.6)
20.	Others	119	11.9
	Total	**1000**	**100**

Table.1: Represents different types of cancers diagnosed among the sample population. out of 1000 population, highest incidence and prevalence was observed for Breast cancer (F= 18%, M= 0.2%; n=182), cervical cancer (F= 17%, M= 0.2%; n= 172), Ovarian cancer (8.6%; n=86), stomach cancer (F= 2%, M= 4.9%; n=69), Lung cancer (F= 2.3%, M= 4.2%; n=65) and the least incidence was for Cervix cancer (1.5%; n= 15), CLL (F= 0.8%, M= 0.6%; n= 14) in both males and females.

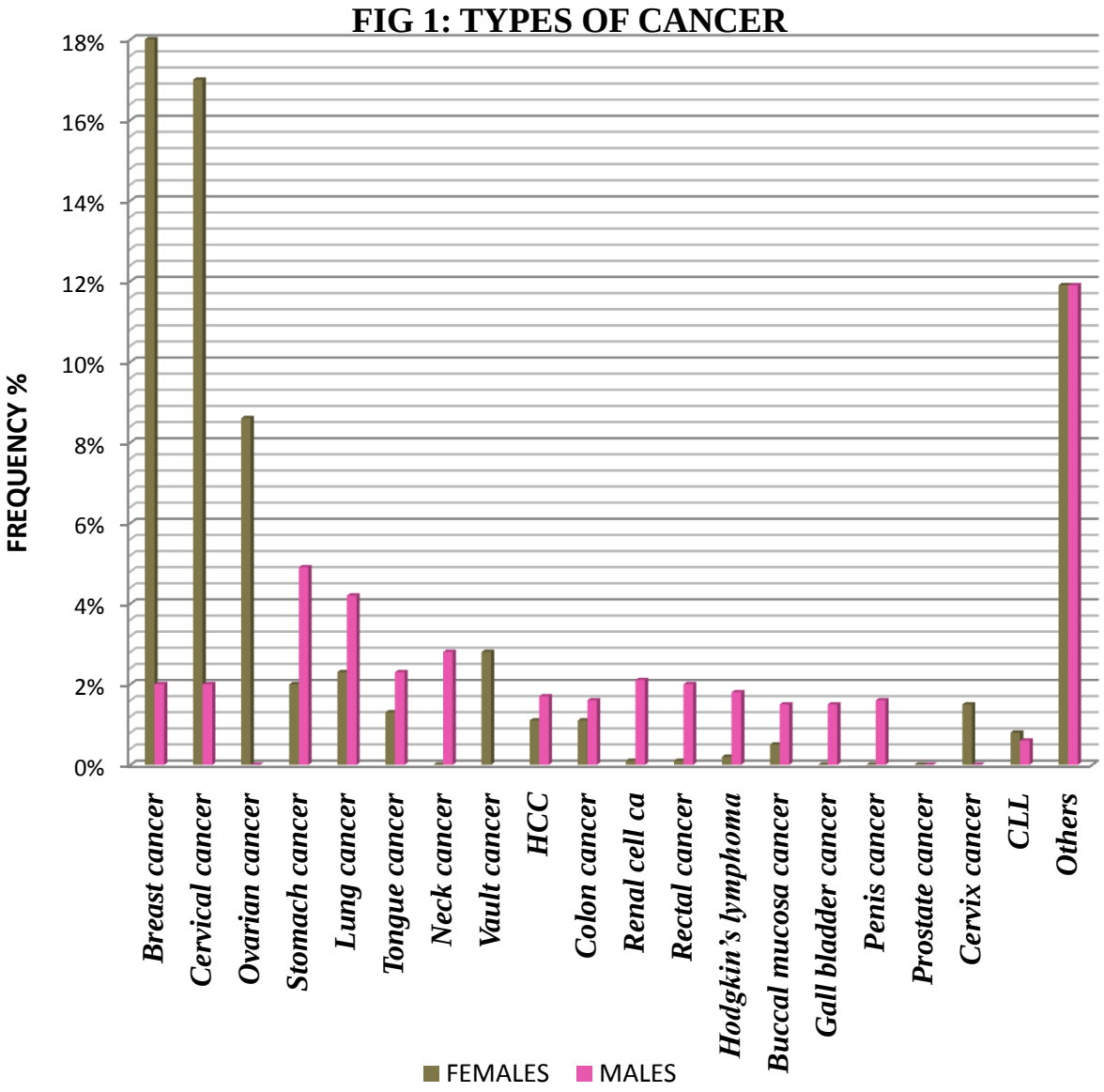


TABLE 2: DISTRIBUTION OF CANCER PATIENTS BASED ON AGE

S.NO	AGE IN YEARS	NO. OF PATIENTS DIAGNOSED WITH CANCER	FREQUENCY (%)
1.	10-20	16	1.6 %
2.	21-30	27	2.7%
3.	31-40	118	11.8%
4.	41-50	272	27.2%
5.	51-60	306	30.6%
6.	61-70	179	17.9%
7.	71-80	77	7.7%
8.	81-90	5	0.5%

TABLE 2 : Out of 1000 people, people with age group is in between 51-60 years (30.6%; n=306), 41-50 years (27.2%; n=272), 61-70 years (17.9%; n=179), 31-40 years (11.8%; n=118) were most commonly affected with different types of cancer and the least affected age groups were 71-80 years (7.7%; n=77), 21-30 years (2.7%; n=27), 10-20 years (1.6%; n=16), 81-90 years (0.5%; n=5). The most affected subjects were with mean age group of 50.4 ± 24.

FIG 2: FREQUENCY DISTRIBUTION OF CANCERS BASED ON AGE

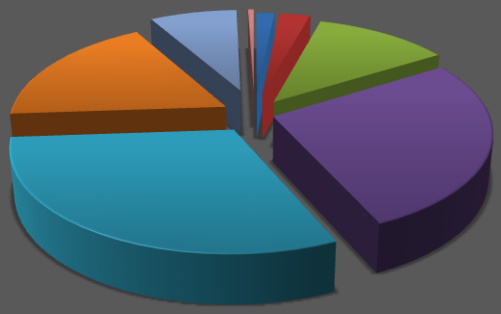


TABLE 3: GENDER WISE DISTRIBUTION

S.NO	GENDER	NO: OF CASES	FREQUENCY (%)
1.	Males	327	32.7
2.	Females	673	67.3

TABLE 3: Based on the Epidemiological survey, out of 1000 Females (67.3%; n=673) were more prone to different types of cancers when compared to Males (32.7%; n=327).

FIG 3: GENDER WISE DISTRIBUTION

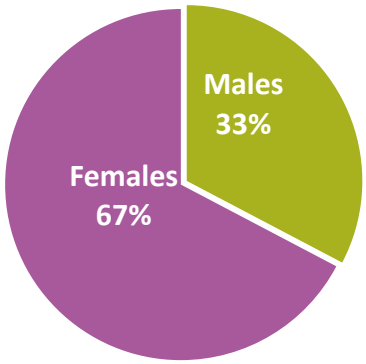
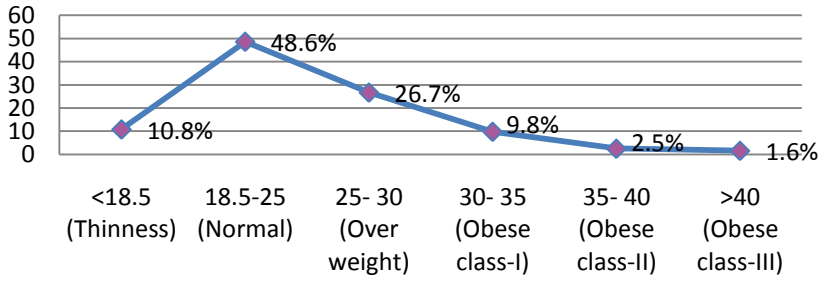


TABLE 4: BMI BASED DISTRIBUTION OF SAMPLE POPULATION

S.NO	BMI		NO. OF PATIENTS WITH BMI	FREQUENCY (%)
1.	<18.5	(Thinness)	108	10.8
2.	18.5-25	(Normal)	486	48.6
3.	25- 30	(Over weight)	267	26.7
4.	30- 35	(Obese class-I)	98	9.8
5.	35- 40	(Obese class-II)	25	2.5
6.	>40	(Obese class-III)	16	1.6

TABLE 4: shows that 13.9% (n=139) subjects were Obese (30-35: Obese class-I, 35-40: Class-II, >40: Class-III), 26.7% (n=267) were found to be Overweight (25-30), 10.8% (n=108) were found to have Low BMI (<18.5) than normal and the 48.6% (n= 486) subjects were within the Normal BMI range (18.5-24.5).

FIG 4: BMI WISE DISTRIBUTION



DETERMINATION OF NATURE AND SEVERITY OF ADR'S

A total of 150 patients who are receiving Chemotherapy were assessed for ADR's using CTCAE scale – 4.0 over a period of 6 months. During which total number of patients were developed atleast one ADR.

TABLE 5: AGE WISE DISTRIBUTION OF STUDY POPULATION

S.NO	AGE GROUP (in years)	NO. OF CASES	PERCENTAGE (%)
1.	0 -10	2	1.3%
2.	11-20	8	5.3%
3.	21-30	10	6.6%
4.	31-40	13	8.6%
5.	41-50	47	31.3%
6.	51-60	40	26.6%
7.	61-70	16	10.6%
8.	71-80	10	6.6%
9.	81-90	4	2.6%

TABLE 5: Out of 150 patients, the ADR'S were frequently reported in people having the age group of 41-50 years (31.3%; n=47), 51-60 years (26.6%; n=40), moderately affected age groups were 61-70 years (10.6%; n=16), 31-40 yeas (8.6%; n=13), 71-80 years & 21-30 years (6.6%; n=10), 11-20 years (5.3%; n=8), and the least affected age groups were 81-90 years (2.6%; n=4), 0-10 years (1.3%; n=2).

FIG 5 : AGE WISE DISTRIBUTION

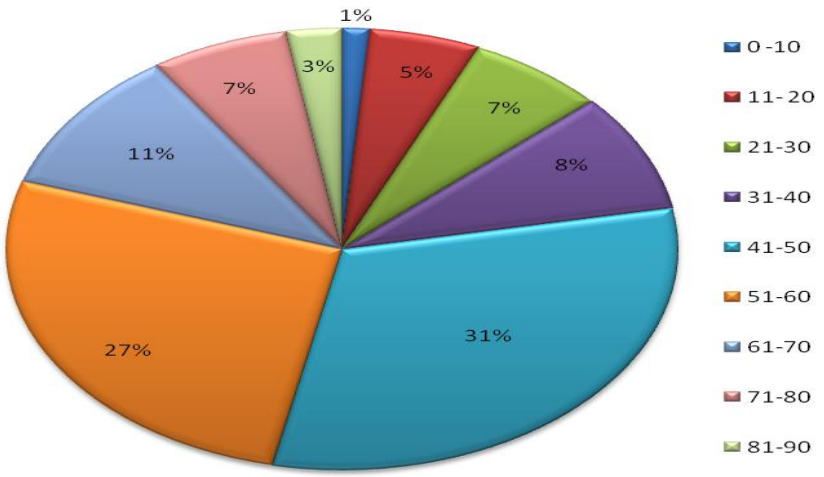


TABLE 6:

S.NO	GENDER	NO.OF CASES	PERCENTAGE (%)
1.	Males	70	46.6%
2.	Females	80	53.3%
	Total	150	100%

TABLE 6: Among the study population, it was found that Females (53.3%; n= 80) were more prone to ADR's when compared to Males (46.6%; n= 70), this may be attributed to Hormonal changes during different stages of life, PK & PD alterations, BSA.

FIG 6 : GENDER WISE DISTRIBUTION

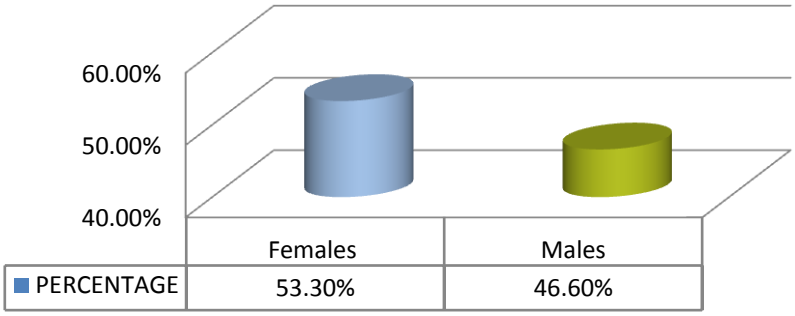


TABLE 7: CATEGORIZATION OF SUBJECTS BASED ON TYPE OF CANCER

S.NO	TYPE OF CANCER	NUMBER OF CASES DIAGNOSED AS	PERCENTAGE (%)
1.	Breast cancer	35	23.3%
2.	Breast cancer with Lung Metastasis	4	2.6%
3.	Ovarian cancer	17	11.3%
4.	Lung cancer	12	8.0%
5.	Stomach cancer	9	6.0%
6.	NHL	7	4.6%
7.	ALL	3	2%
8.	ALL cancer with lung Metastasis	2	1.3%
9.	CLL	5	3.3%
10.	Hodgkin's Lymphoma	4	2.6%
11.	HL with liver Metastasis	1	0.6%
12.	Ewing sarcoma	4	2.6%
13.	Cervical cancer	4	2.6%
14.	Seminoma	3	2.0%
15.	Seminoma cancer with liver Metastasis	1	0.6%
16.	Colon cancer	4	2.6%
17.	Cervix cancer	3	2.0%
18.	Ca. Nasopharynx	3	2.0%
19.	Buccal Mucosa	2	1.3%
20.	CML	1	0.6%
21.	CML with Metastasis of liver and spleen	1	0.6%
22.	Hepatocellular Carcinoma	2	1.3%
23.	Synovial sarcoma	2	1.3%
24.	AML	2	1.3%
25.	Ca. Tongue	2	1.3%
26.	Multiple Myeloma	2	1.3%
	Others		
27.	Choriocarcinoma	1	0.6%
28.	Bladder cancer	1	0.6%
29.	Ca. Cecum	1	0.6%
30.	Osteosarcoma	1	0.6%
31.	Medulloblastoma	1	0.6%
32.	Ca. Vault	1	0.6%
33.	Ca. Hypopharynx	1	0.6%
34.	Ca. Periampullary	1	0.6%
35.	Pancreatic cancer	1	0.6%
36.	Pancreatic cancer with liver Metastasis	1	0.6%
37.	Skin sarcoma	1	0.6%
38.	Pleomorphic sarcoma	1	0.6%

39.	Ca. Endometrium	1	0.6%
40.	Gallbladder cancer	1	0.6%

TABLE 7: Out of 150 population, highest incidence of ADR's was seen in patients undergoing treatment for Breast cancer (26%; n=39) followed by Ovarian cancer (11.3%; n=17), Lung cancer (8%; n=12), Stomach cancer (6%; n=9), NHL (4.6%; n=7) and the least incidence of ADR's were seen in patients undergoing treatment with different drugs in different cancers like Choriocarcinoma (0.6%; n=1), Bladder cancer (0.6%; n=1), Ca. Cecum (0.6%; n=1), Osteosarcoma (0.6%; n=1), Medulloblastoma (0.6%; n=1), Ca. Vault (0.6%; n=1), Ca. Hypopharynx (0.6%; n=1), Ca. Periampullary (0.6%; n=1), Pancreatic cancer with liver Metastasis (0.6%; n=1), Skin sarcoma (0.6%; n=1), Pleomorphic sarcoma (0.6%; n=1), Ca. Endometrium (0.6%; n=1), Gallbladder cancer (0.6%; n=1).

FIG 7 : CATEGORIZATION OF SUBJECTS BASED ON TYPES OF CANCER

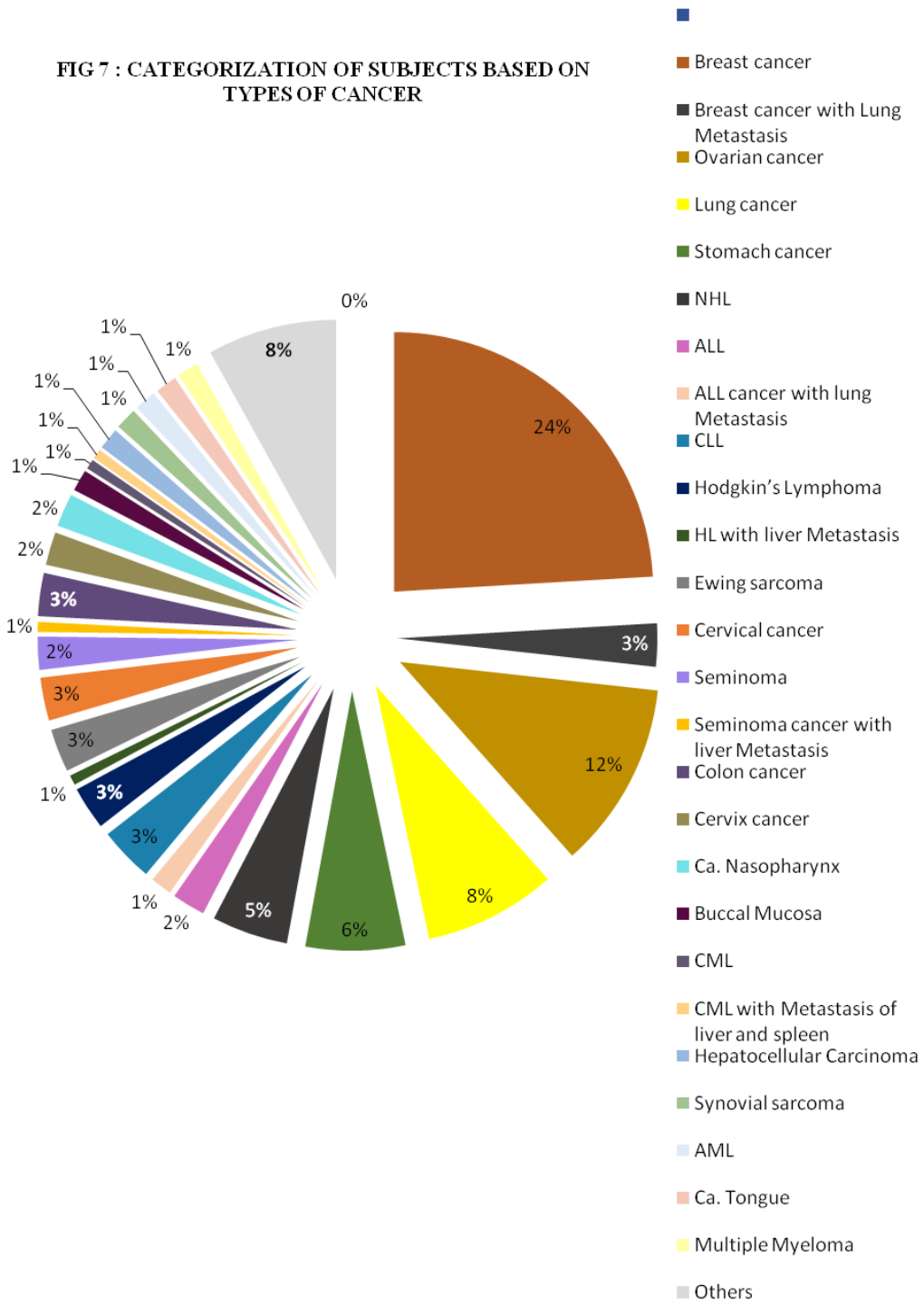


TABLE 8: COMMONLY PRESCRIBED CHEMOTHERAPEUTIC DRUGS

S.NO	COMMONLY PRESCRIBED DRUGS	NO: OF CASES	PERCENTAGE (%)
1.	Cyclophosphamide & Adriamycin	47	31.3%
2.	5-FU	36	24.0%
3.	Paclitaxel	27	18.0%
4.	Cisplatin	26	17.3%
5.	Carboplatin	22	14.6%
6.	Vincristine	20	13.3%
7.	Rituximab	10	6.6 %
8.	Methotrexate	7	4.6%
9.	Bevacizumab	4	2.6%
10.	Trastuzumab	3	2.0%

TABLE 8: represents the commonly prescribed chemotherapeutic drugs in patients undergoing cancer chemotherapy. Out of 150 patients, maximum no: of patients were undergoing treatment with Cyclophosphamide and Adriamycin (31.3%; n= 47), 5- FU (24%; n= 36), Paclitaxel (18%; n= 27), platinum compounds like cisplatin and Carboplatin (17.3% & 14.6%) and the least were prescribed with targeted agents like Bevacizumab (2.6%; n=4) & Trastuzumab (2%; n=3) as a mono and dual therapy. All of these patients developed atleast one type of ADR with different grades.

FIG 8: PRESCRIBING PATTERNS OF CHEMOTHERAPEUTIC DRUGS

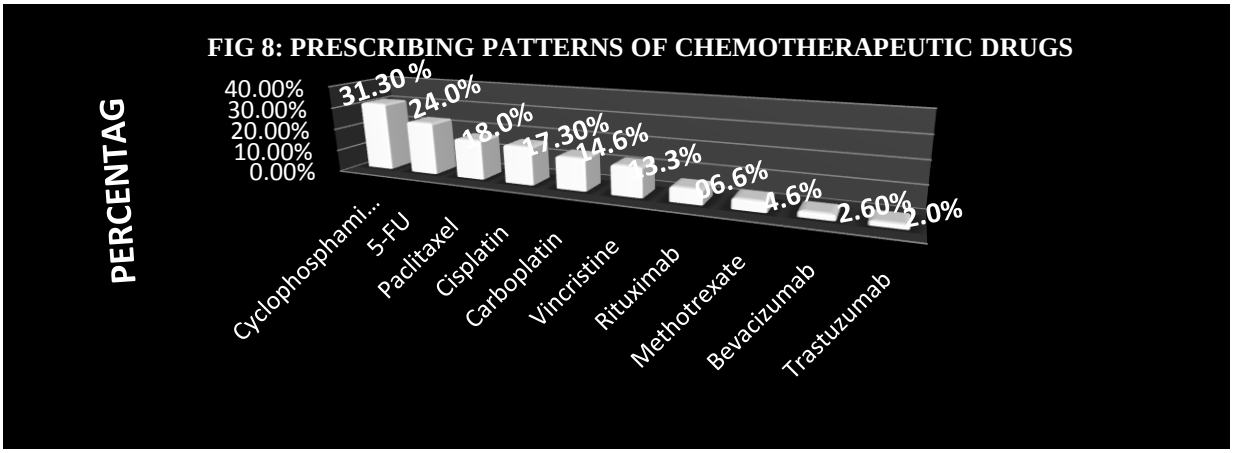


TABLE 9: PRESCRIBING PATTERNS OF CHEOTHERAPEUTIC REGIMEN

S.NO	THERAPEUTIC REGIMEN	NO.OF CASES	PERCENTAGE (%)
1.	Paclitaxel + Carboplatin	17	11.3%
2.	Adriamycin + 5-FU + Cyclophosphamide	16	10.6%
3.	Adriamycin + Cyclophosphamide	11	7.3%
4.	Cisplatin + 5-FU	9	6%
5.	Bendamustine + Rituximab	6	4%
6.	Cisplatin	5	3.3%
7.	Adriamycin+ Cyclophosphamide +Docetaxel	5	3.3%
8.	Gemcitabine + Capecitabine	4	2.6%
9.	Premetrexed + Cisplatin	4	2.6%
10.	Vincristine + Adriamycin + Cyclophosphamide + Etoposide+ Ifosfamide + MESNA	4	2.6%
11.	Oxaliplatin + Leucovorin + 5-FU	4	2.6%
12.	Epirubicin + Oxaliplatin + Capecitabine	3	2.0%
13.	Trastuzumab + Docetaxel	2	1.3%
14.	Vincristine + Daunorubicin	2	1.3%
15.	Erlotinib	2	1.3%
16.	Cyclophosphamide + Vincristine + Rituximab	2	1.3%
17.	Gemcitabine + Bevacizumab + Carboplatin + Paclitaxel	2	1.3%
18.	Adriamycin + Bleomycin + Vincristine +Dacarbazine	2	1.3%
19.	Vincristine + Daunorubicin + 6-Mercaptopurine + Cytarabine +	2	1.3%

	Methotrexate + Prednisone		
20.	Epirubicin + Oxaliplatin + Capecitabine	2	1.3%
21.	5-FU + Leucovorin	2	1.3%
22.	Daunorubicin + Vincristine + Asparginase + Methotrexate + Prednisone	2	1.3%
23.	Etoposide + Cisplatin	2	1.3%
24.	Paclitaxel	2	1.3%
25.	Gemcitabine + Doxorubicin + Paclitaxel	2	1.3%
26.	Cisplatin + Etoposide + Premetrexed	2	1.3%
27.	Oxaliplatin + Capecitabine	2	1.3%
		32	19.2%
OTHERS			
28.	Cisplatin + Etoposide + Bleomycin	1	0.6%
29.	Rituximab + Cyclophosphamide + Doxorubicin + Vincristine	1	0.6%
30.	Bortezomib + Lenalidomide	1	0.6%
31.	Sorafenib	1	0.6%
32.	5FU + Adriamycin + Cyclophosphamide + Trastuzumab	1	0.6%
33.	Vincristine + Daunorubicin + 6-Mercaptopurine + Methotrexate + Cytarabine + Cyclophosphamide	1	0.6%
34.	Doxorubicin + Bevacizumab	1	0.6%
35.	Methotrexate + Dactinomycin + Etoposide + Vincristine + Leucovorin+ Cyclophosphamide	1	0.6%
36.	Cyclophosphamide + 5-FU + Docetaxel + Trastuzumab + Adriamycin	1	0.6%
37.	Paclitaxel + Cyclophosphamide + Adriamycin	1	0.6%
38.	Gemcitabine+Carboplatin	1	0.6%
39.	Oxaliplatin+5FU	1	0.6%
40.	Premetrexed+Paclitaxel+Carboplatin	1	0.6%
41.	Vincristine + Daunorubicin + Methotrexate + Asparginase + Prednisone	1	0.6%
42.	Rituximab + Cyclophosphamide + Adriamycin + Vincristine + Daunorubicin + Prednisone	1	0.6%
43.	Lenalidomide + Bortezomib	1	0.6%
44.	Gemcitabine + Paclitaxel + Carboplatin	1	0.6%
45.	5-FU	1	0.6%
46.	Adriamycin + Ifosfamide + HLX	1	0.6%
47.	Adriamycin + Cyclophosphamide + Paclitaxel	1	0.6%
48.	Docetaxel + Cyclophosphamide	1	0.6%
49.	Capecitabine + Irinotecan	1	0.6%
50.	Docetaxel + 5-FU+ Cisplatin	1	0.6%
51.	Oxaliplatin + Capecitabine	1	0.6%
52.	Bevacizumab	1	0.6%
53.	Imatinib	1	0.6%
54.	Adriamycin+ Dacarbazine + Ifosfamide	1	0.6%
55.	Gemcitabine + Oxaliplatin	1	0.6%
56.	Daunorubicin + Cytarabine	1	0.6%
57.	Adriamycin	1	0.6%
58.	Cisplatin + Adriamycin	1	0.6%
59.	Lomustine+ Cisplatin+ Vincristine	1	0.6%

TABLE 9: Among 150 population, maximum no. of people were prescribed with Paclitaxel+ Carboplatin (11.3%; n=17) followed by Adriamycin+ 5-FU+ Cyclophosphamide (10.6%; n=16), Adriamycin + Cyclophosphamide (7.3%; n=11), Cisplatin+5FU (6%; n=9), Bendamustine + Rituximab (4%; n=6), Adriamycin +Cyclophosphamide +Docetaxel (3.3%; n=5), Gemcitabine + Capecitabine, Premetrexed + Cisplatin, Vincristine + Adriamycin + Cyclophosphamide + Etoposide+ Ifosfamide + MESNA, Oxaliplatin + Leucovorin + 5-FU (n=4; 2.6%) which are most offending drugs for causing Adverse drug reactions in the patients and others were least commonly prescribed

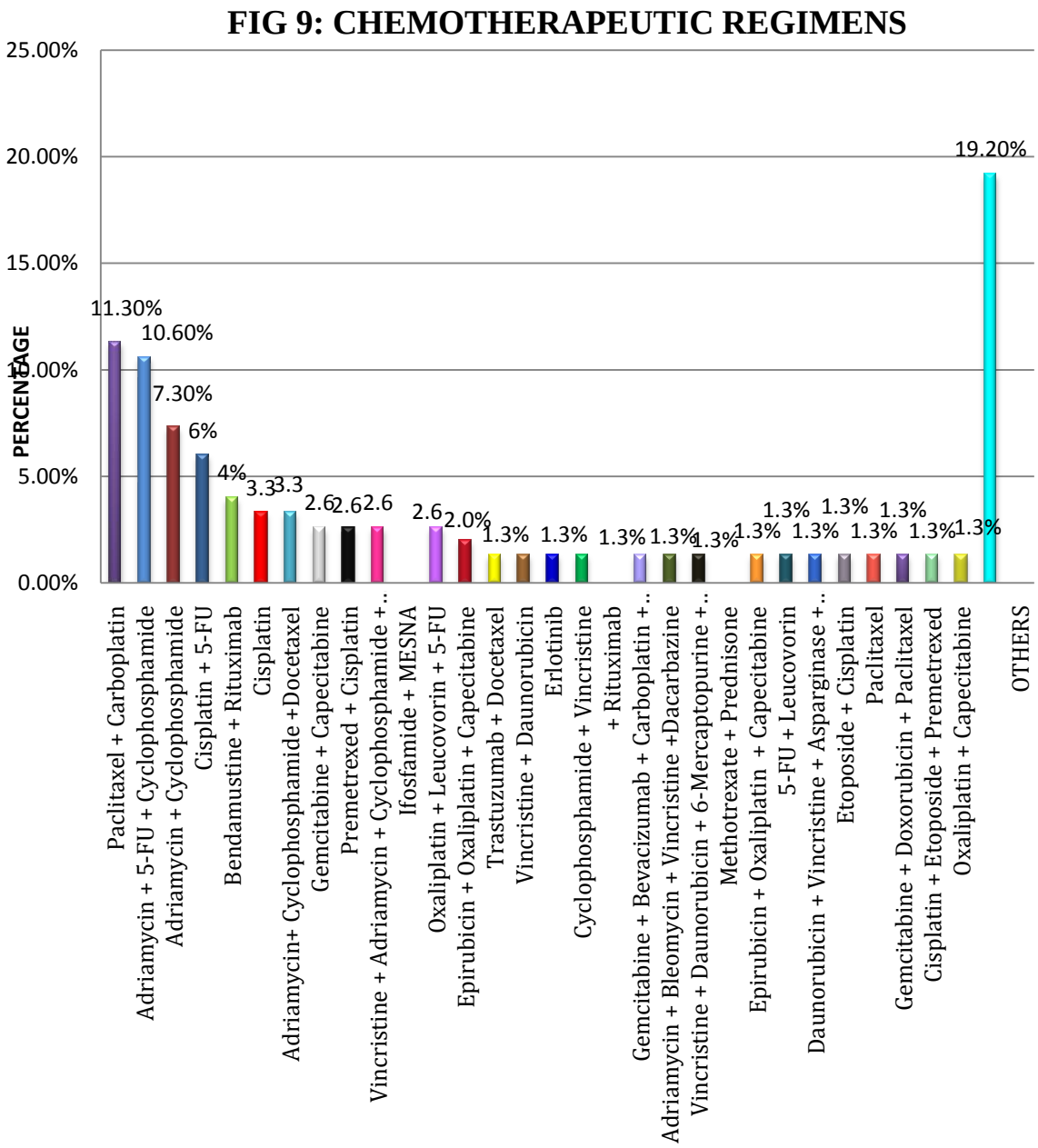


TABLE 10: ADVERSE DRUG REACTION PATTERN AMONG SUBJECTS WHO ARE ON CHEMOTHERAPY

S.NO	SAMPLE SIZE	NUMBER OF CASES EXPOSED TO ADR'S	PERCENTAGE (%)
1.	Patients receiving Cancer Chemotherapy	150	100%
2.	No.of patients with common ADR's	123	82%
3.	No.of patients with rare ADR's	27	18%

TABLE 10: During the study period, 150 patients were received various classes of chemotherapeutic agents for the treatment of their malignant conditions, among these 123 (82%) patients were exposed to common ADR's and the less number of subjects (8%; n=27) were exposed to Rare ADR's.

FIG 10: SAMPLE SIZE DISTRIBUTION

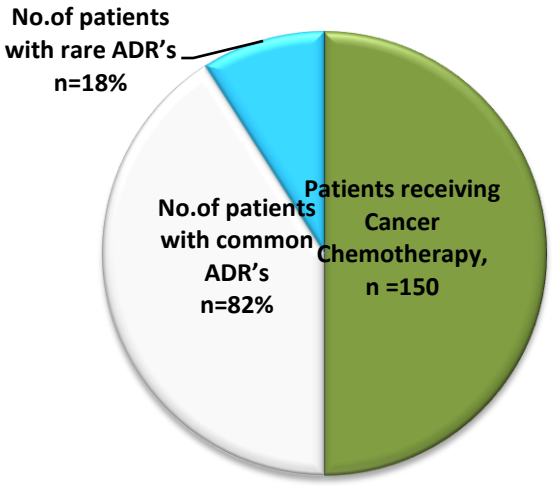


TABLE 11: OFFENDING DRUGS FOR RARE ADR'S

S.NO	RARE ADR'S IDENTIFIED	OFFENDING DRUGS	NO.OF PATIENTS EXPOSED	PERCENTAGE (%)
1.	Cyanosis	5-FU, Cyclophosphamide, Adriamycin, Vincristine	24	16.0%
2.	Black spots on hands and legs	Sorafenib	1	0.6%
3.	Blackish discolouration of tongue	Adriamycin, Cyclophosphamide, Vincristine	5	3.3%
4.	White spots on face	Carboplatin	4	2.6%

TABLE 11: Among the study population, Very few drugs like Sorafenib, Adriamycin, Cyclophosphamide, Vincristine, 5- FU & Carboplatin developed Uncommon ADR's such as Cyanosis (16.0%; n=24), Black discolouration of tongue (3.3%; n= 5), White spots on face (2.6%; n=4), Black spots on hands and legs (0.6%; n=1).

FIG 11: RARE ADR'S IDENTIFIED

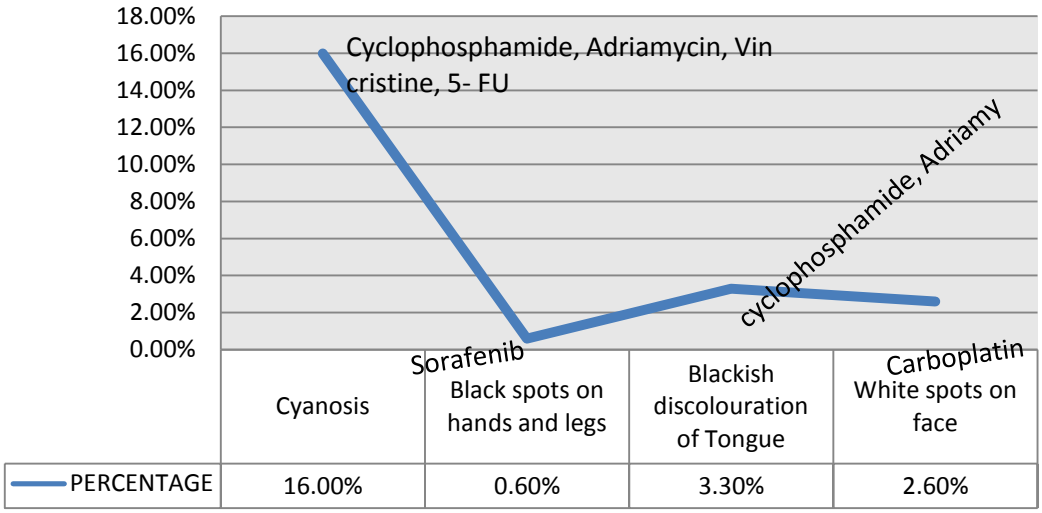


TABLE 12: SEVERITY ASSESSMENT OF ADR'S ACCORDING TO CTCAE VERSION 4.0

S.NO	GRADE	NO.OF CASES EXPOSED WITH ADR	PERCENTAGE (%)
1.	GRADE- I (Mild)	488	51.5%
2.	GRADE- II (Moderate)	423	44.6%
3.	GRADE- III (Severe)	35	3.7%
4.	GRADE- IV (Life threatening)	2	0.2%
	TOTAL	948	100%

TABLE 12: In overall study period, a total of 948 ADR's with different grades were identified. In that max number of people affected with Grade- I ADR's (51.5%; n= 488), Grade- II (44.6%; n=423), and very few people were developed with Grade III (3.7%; n= 35) and Grade IV ADR's (0.2%; n=2).

FIG 12 : SEVERITY ASSESSMENT OF ADR'S

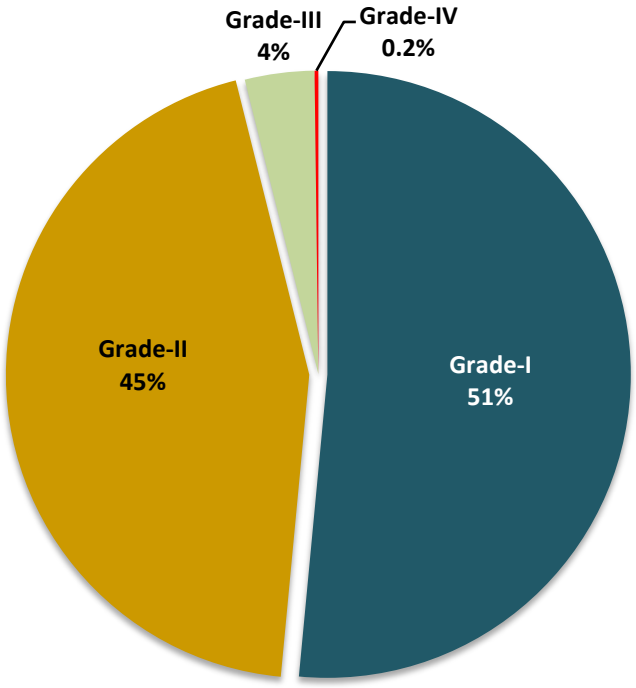


TABLE 13: ANATOMICAL CLASSIFICATION OF ADR'S

S.NO	ORGAN SYSTEM INVOLVED	NO. OF CASES PRONE TO ADR'S	PERCENTAGE (%)
1.	Haematological system	137	91.3%
2.	Nervous system	51	34.0%
3.	Cardiovascular system	20	13.3%
4.	Respiratory system	36	24.0%
5.	Gastro-intestinal system	135	90.0%
6.	Hepatic system	96	64.0%
7.	Dermatological system	107	71.3%
8.	Renal system	26	17.3%

TABLE 13: In the total study population, highest incidence of ADR's were observed related to Haematalogical system (91.3%; n=137), followed by Gastro-intestinal system (90%; n=135), Dermatological system (71.3%; n=107), Hepatic system (64%; n=96), Neurological system (34%; n=51), Respiratory system (24%; n=36), Renal system (17.3%; n=26) and the least no: of ADR's were associated with Cardiovascular system (13.3%; n=20).

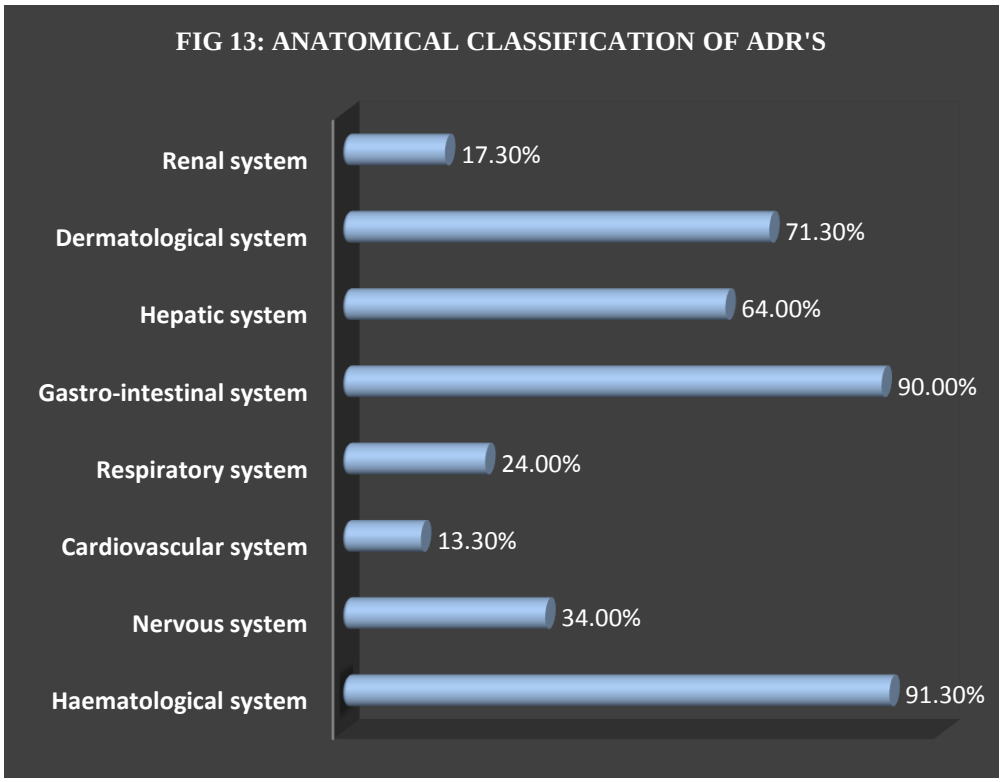


TABLE 14: GENDER BASED COMPARISON OF ADR'S BY USING STATISTICAL ANALYSIS

S.NO	RARE ADR'S IDENTIFIED	MALES	FEMALES	PERCENTAGE (%)		
				M	FM	
1.	Cyanosis	4	20	2.6	13.3	T-TEST VALUE **2.100** P- VALUE **0.0251**
2.	Discolouration of skin	6	14	4.0	9.3	
3.	Blackish discolouration of tongue	3	2	2.0	1.3	
4.	White spots on face	2	2	1.3	1.3	
5.	Menstrual irregularities	0	1	0	0.6	
6.	Fainting	0	1	0	0.6	
7.	Hypochloremia	0	7	0	4.6	
8.	Hyperglycaemia	2	6	1.3	4.0	
9.	Nephrotoxicity	3	6	2.0	4.0	
10.	Myalgia	1	1	0.6	0.6	
MEAN		**2.1**	**6**			

S.NO	COMMON ADR'S IDENTIFIED	MALES	FEMALES	PERCENTAGE (%)		
				M	FM	
1.	Vomitings	42	60	28.0	40.0	
2.	Nausea	29	40	19.3	26.6	
3.	Diarrhoea	11	23	7.30	15.3	T-TEST
4.	Anorexia	14	28	9.30	18.6	VALUE
5.	Wt. Loss	12	17	8.0	11.3	**2.021**
6.	Anaemia	26	35	17.3	23.3	P- VALUE
7.	Decreased platelet count	12	16	8.0	10.6	**0.0275**
8.	Leukopenia	10	16	6.6	10.6	
9.	Neutropenia	6	9	4.0	6.0	
10.	Increased hepatic enzyme	11	22	7.3	14.6	
11.	Hyperglycemia	13	20	8.6	13.3	
12.	Hyperalbuminemia	10	19	6.6	12.6	
13.	Fatigue	14	32	9.3	21.3	
14.	Body pains	5	13	3.3	8.6	
15.	Edema	3	8	2.0	5.3	
16.	Peripheral neuropathy	26	14	17.3	9.3	
17.	Drowsiness	9	20	6.0	13.3	
18.	Headache	4	11	2.6	7.3	
19.	Hyponatremia	8	18	5.3	12.7	
20.	Mucositis	5	4	3.3	2.6	
21.	Alopecia	17	29	11.3	19.3	
MEAN		**13.67**	**21.62**			

TABLE 14: shows the Common and rare ADR's that were identified among the sample population. Difference between males and females were assessed by using statistical analytic tests like T- test, mean and probability testing which shows that there is a significant difference between males and females. Among the study population, mostly ADR's were reported in females with highest incidence because of various factors which involves all anatomical systems.

TABLE 15: SEVERITY ASSESSMENT OF ADR's ACCORDING TO CTCAE SCALE- 4.0

Organ system	ADR's Involved	Grade-I	Grade-II	Grade-III	Grade-IV	No. of cases	Percentage (%)
GI system	Vomitings	46	50	6	-	102	32.9%
	Nausea	39	30	-	-	69	22.2 %
	Anorexia	15	19	-	-	34	10.9 %
	Diarrhea	10	25	7	-	42	13.5 %
	Constipation	12	11	-	-	23	7.4 %
	Weight loss	27	2	-	-	29	9.3 %
	Abdominal pain	11	-	-	-	11	3.5 %
Total	**7**	-	-	-	-	**310**	**99.7 %**
Blood	Anemia	25	26	10	-	61	36.9%
	Thrombocytopenia	12	10	5	1	28	16.9%
	Leukocytopenia	13	11	1	1	26	15.7%
	Neutropenia	9	8	3	-	20	12.1%
	Thrombocytosis	9	4	-	-	13	7.42%
	Neutrophilia	8	3	-	-	11	6.28%
	Eosinophilia	6	-	-	-	6	3.42%
Total	**7**	-	-	-	-	**165**	**98.72%**
Hepatic system	Increased level of Hepatic enzymes	20	12	1	-	33	32.6%
	Hyperglobulinemia	15	18	-	-	33	32.6%
	Hypoalbuminemia	14	15	-	-	29	28.7%
	Icterus	3	-	-	-	3	2.97%

	Ascites	3	-	-	-	3	2.97%
Total	**5**	-	-	-	-	**101**	**99.84%**
Unspecific	Fatigue	22	24	-	-	46	37.1%
	Body pains	7	11	-	-	18	14.5%
	Nephrotoxicity	7	2	-	-	9	7.2%
	Edema	4	7	-	-	11	8.8%
	Sore throat	3	5	-	-	8	6.4%
	CVS toxicity	5	2	-	-	7	5.6%
	Sweating	4	1	-	-	5	4.0%
	Hyperglycemia	4	3	1	-	8	6.4%
	Tonsillitis	2	1	-	-	3	2.4%
	Myalgia	1	1	-	-	2	1.6%
	Rigidity	1	-	-	-	1	0.8%
	Pus in belly	1	-	-	-	1	0.8%
	Pain during Micturition	1	-	-	-	1	0.8%
	Pain during passing stools	1	-	-	-	1	0.8%
	Menstrual irregularities	1	-	-	-	1	0.8%
Total	**16**	-	-	-	-	**124**	**99.6%**
Skin	Discolouration of skin	11	9	-		20	17.85%
	Cyanosis	13	11	-	-	24	21.4%
	Alopecia	24	22	-	-	46	41.07%
	Blackish coloration of Tongue	4	1	-	-	5	4.4%
	White spots on face	1	3	-	-	4	3.57%
	Allergies	7	6	-	-	13	11.6%
Total	**6**	-	-	-	-	**112**	**99.89%**
Nervous System	Peripheral Neuropathy	19	20	-	-	40	50%
	Headache	8	7	-	-	15	18.7%
	Drowsiness	9	10	-	-	19	23.7%
	Insomnia	3	2	-	-	5	6.25%
	Fainting	-	1	-	-	1	0.12%
Total	**6**	-	-	-	-	**80**	**98.7%**
Electrolyte Imbalance	Hyponatremia	12	14	-	-	26	72.2%
	Hypernatremia	3	1	-	-	4	11.1%
	Hypokalemia	2	1	-	-	3	8.3%

	Hypokalemia	1	1	-	-	2	5.55%
	Hypochloremia	1	-	-	-	1	2.77%
Total	**5**	-	-	-	-	**36**	**99.92%**
Oral Cavity	Mucositis	4	5	-	-	9	69.2%
	Oral candidiasis	1	3	-	-	4	30.7%
Total	**2**	-	-	-	-	**13**	**99.9%**
Ophthalmological system	Burning sensation of eyes	2	3	-	-	5	55.5%
	Blurred vision	1	1	-	-	2	22.2%
	Pain of eyes	1	1	-	-	2	22.2%
Total	**3**	-	-	-	-	**9**	**99.9%**

TABLE 15: Represents the pattern of ADR's developed among the patients. In overall study period, all the subjects developed ADR's with different grades related to various organ systems. In that, maximum number of ADR's experienced was related to GI system (A total of 310 ADR's with different grades) i.e. Vomitings (Grade I- 46, Grade II- 50, Grade III- 6), Nausea (Grade I- 39, Grade II- 30), Anorexia (Grade I- 15, Grade II- 19), Diarrhea (Grade I- 10, Grade II- 25, Grade III- 7), Constipation (Grade I- 12, Grade II- 11), Weight loss (Grade I- 27, Grade II- 2), Abdominal pain (Grade-11) and the least were identified related to Ophthalmological system(A total of 9 ADR's with different grades) i.e. Burning sensation of eyes (Grade I- 2, Grade II- 3), Blurred vision (Grade I- 1, Grade II- 1), Pain of eyes (Grade I- 1, Grade II-1).

IV. Discussion

In our study, we educated patients regarding medications, Dietary and Lifestyle modifications by using PILs. A total of 1000 study population were reviewed and quantified the proportion of cancer burden in different age groups, Genders and subjects whose BMI is more than the normal ranges over a period of 6 months. Regarding the type of cancers, out of 1000 population, highest incidence and prevalence was observed for Breast cancer (F= 18%, M= 0.2%; n=182), cervical cancer (F= 17%, M= 0.2%; n= 172), Ovarian cancer (8.6%; n=86), Cervix cancer (1.5%; n=15), Vault cancer (2.8%; n=28) in females due to Hormonal status, Chronic infections, Overweight and Obesity, Low BSA and Less Physical activities, whereas highest incidence of Stomach cancer (M- 4.9%, F- 2%; n= 69), Lung cancer (M= 4.2%, F= 2.3% ; n=65), Neck cancer (M= 2.8%; n=28), Tongue cancer (M= 2.3%, F- 1.3%; n=36), Renal cell carcinoma (M= 2.1%, F- 0.1%; n=22), Rectal cancer (M= 2.0%, F- 0.1%; n=21), Hodgkin's Lymphoma (M= 1.8%, F- 0.2%; n=20) and other type of cancers **(as shown in Table.1; Fig.1)** were most commonly diagnosed cancers in males due to Social habits like cigarette smoking, Tobacco chewing, Alcohol consumption, Unhealthy lifestyle, Occupational risk.

Regarding the Distribution of cancers based on demographic profile of the subjects, epidemiological status shows that the subjects whose age group is in between 51-60 years (30.6%; n=306), 41-50 years (27.2%; n=272), 61-70 years (17.9%; n=179), 31-40 years (11.8%; n=118) were most commonly affected with different types of cancer and the least affected age groups were 71-80 years (7.7%; n=77), 21-30 years (2.7%; n=27), 10-20 years (1.6%; n=16), 81-90 years (0.5%; n=5) (**shown inTable.2; Fig.2).** The most affected subjects were with mean age group of 50.4 ± 24.6.

Based on the Epidemiological survey, Females (67.3%; n=673) were more prone to different types of cancers when compared to Males (32.7%; n=327) **(Table.3; Fig.3)** due to Hormonal status, Chronic infections, Overweight and Obesity, Low BSA and Less Physical activities [65].

From the Epidemiological study, out of total study population results shows that maximum number of people were found to have Normal BMI (48.6%; n=486), 26.7% of people have BMI >25 (Overweight) **(shown in Table.4; Fig.4)**.

So, to treat different types of cancers, various categories of chemotherapeutic drugs have to be used either as monotherapy or as combinational therapy. Most of these Anti-neoplastic agents are narrow therapeutic index drugs which have a greater potential to cause ADR's. So, we have included a total of 150 study population who have developed atleast one ADR due to chemotherapy to determine the role of pharmacist in Monitoring and spontaneous reporting of ADR's for a period of 6 months.

The demographic profile of present study showed that ADR's were frequently observed in the subjects whose age group of 41-50 years (31.3%; n=47), 51-60 years (26.6%; n=40), and the least affected age groups were 81-90 years (2.6%; n=4), 0-10 years (1.3%; n=2). The mean age group exposed to ADR's was found to be

45.4 ± 27.47 years because of their diminished metabolizing capacity and excretory functions and also changes in PK and PD characteristics along with increasing age **(as shown in Table.5; Fig.5).**

Among all the people involved in the study, Females (53.3%; n=80) were majorly prone to ADR's when compared to Males (46.6%,n=70) due to hormonal changes, increased Bio-availability, greater sensitivity to medications, lower body weight, lower organ sizes, higher percentage of body fat, smaller BSA that contributes to altered PK responses to drugs [58, 61] **(Table.6; Fig.6)**.

In agreement to other studies, highest incidence of ADR's were seen in patients undergoing treatment for Breast cancer (26%, n=39) followed by Ovarian cancer (11.3%, n=17), Lung cancer (8%, n=12), Stomach cancer (6%, n=9) **(as shown in Table.7; Fig.7)**.

From our research, it was found that Cyclophosphamide & Adriamycin (31.35, n=47), 5FU (24%, n=36), Paclitaxel (185, n=27), Cisplatin (17.3%, n=26), Carboplatin (14.6%, n=22),Vincristine (13.35, n=20), Rituximab (6.65, n=10) , Methotrexate (4.6%, n=7), Bevacizumab (2.6%, n=4) and Trastuzumab (2%, n=3) were most offending drugs to cause ADR's frequently in study population **(shown in Table.8; Fig.8)**.

Regarding the prescribing patterns of antineoplastic drug regimens, 11.3% (n=17) of patients were received a combination of Paclitaxel + Carboplatin to treat different types of cancers. 10.6% (n=16) of patients were under Adriamycin + cyclophosphamide + 5FU, Adriamycin + Cyclophosphamide (7.3%, n=11), Cisplatin + 5FU (6%,n=9), Bendamustine + Rituximab (4%, n=6), Cisplatin(3.35,n=5), Adriamycin + cyclophosphamide + Docetaxel (3.3%, n=5), Gemcitabine + Capecitabine (2.6%, n=2.6%), Pemetrexed + Cisplatin (2.6%, n=4) **(Table.9; Fig.9)**.

During the study period, 150 patients were received various classes of chemotherapeutic agents for the treatment of their malignant conditions, among these 123 (82%) patients were exposed to ADR's due to PK and PD characteristics, patient factors, Lifestyle changes; and the less number of subjects (8%; n=27) were exposed to rare ADR's because of targeted therapy [59] **(shown in Table.10; Fig.10)**.

Among 150 population, about 82% (n=123) patients have experienced common ADR's and remaining 18% (n=27) people have detected with rare ADR's such as Cyanosis (16%, n=24) followed by Blackish discolouration of skin (3.3%, n=5),White spots on face (2.6%, n=4) and Black spots on hands and legs (0.6%, n=1).These uncommon ADR's were seen in the patients who have received Carboplatin, 5-FU, Adriamycin ,Vincristine ,Sorafenib ,Cyclophosphamide **(Table.11; Fig.11).** To compare the incidence of common, rare ADR's between male and female patients, the collected data was analyzed using unpaired T- test for categorical variables as appropriate. Frequencies and percentages or mean and standard deviation were used to describe the exposure to ADR's among the study population. When common ADR's to Anticancer chemotherapy were considered, females were likely to experience a reaction than males and the difference were found to be statistically significant with a P -Value of 0.0275, on the other hand, a P- value of 0.0251 was obtained in case of rare ADR's between the study groups which was found to be statistically significant **(Table.14; Fig.14)**

By using the severity assessment scale (CTCAE 4.0), ADR's were categorized in to different Grades. Among which majority of the reactions fall under Grade-I (Mild, 51.5%, n=488), Grade – II (Moderate 44.6%, n=423) which don't warrant stopping or changing of drugs but few reactions were categorized under Grade-III (3.7%, n=35) which were considered to be severe and reactions of Grade-IV (0.2%, n=2) **(Table.12; Fig.12)** were least commonly observed which pose the patients to life-threatening situations.

In relation to organ systems, Hematological system (91.3%, n=137), GIT (90%, n=130), Dermatological system (71.3%, n=107) were the anatomical systems which were mostly affected by the ADR's occurred to the chemotherapeutic drugs. Least affected systems were Hepatic system (64%, n=96), CNS (34%, n=51), Respiratory system (24%, n=36), Renal system (17.3%, n=26) and CVS (13.3%, n=20) **(Table.13; Fig.13)**. Our results were consistent with previous studies conducted by **SAPAN KUMAR BEHERA (2017)** *et al* and the study findings revealed that 24.22% of reactions were related to Blood, followed by 14.17% was related to GI.

Among the reported ADR's, most common findings were Alopecia (41.7%, n=46) , Anemia (36.9%, n=61), vomitings (32.9%, n=102), Nausea (22.2%, n=69), Peripheral neuropathy (50%, n=40), Increased level of Hepatic enzymes (32.6%, n=33), Hyperglobulinemia (32.6%, n=33), Hypoalbuminemia (28.7%, n=29), Hyponatremia (72.2%, n=26), Discoloration of skin (17.85%, n=20) which is similar to that of studies conducted by **SHRUTHI SINGH (2019)** *et al*. This study reveals that of the many reactions observed about 63% of patients have experienced nausea, vomiting, alopecia, constipation, diarrhea, Peripheral nervous system manifestations

In overall study period, all the subjects developed ADR's with different grades related to various organ systems. In that, maximum number of ADR's experienced was related to GI system (A total of 310 ADR's with different grades) i.e. Vomitings (Grade I- 46, Grade II- 50, Grade III- 6), Nausea (Grade I- 39, Grade II- 30), Anorexia (Grade I- 15, Grade II- 19), Diarrhea (Grade I- 10, Grade II- 25, Grade III- 7), Constipation (Grade I- 12, Grade II- 11), Weight loss (Grade I- 27, Grade II- 2), Abdominal pain (Grade-11) and the least were identified related to Ophthalmological system (A total of 9 ADR's with different grades) i.e. Burning sensation

of eyes (Grade I- 2, Grade II- 3), Blurred vision (Grade I- 1, Grade II- 1), Pain of eyes (Grade I- 1, Grade II-1) **(as shown in Table.15; Fig.15)** .

V. Conclusion

Cancer Chemotherapeutic drugs have Narrow Therapeutic Index and have a high propensity to cause ADR's. Hence, early detection and voluntary reporting of ADR's (Onco- Pharmacovigilance) may minimize the harm either by modifying the dose or changing the offending drug with a suitable alternative. With the aim of improving patient's QOL and to reduce Hospitalization, treatment cost due to the ADR's, we educated patients about medications usage and its side effects, Dietary modifications, Lifestyle changes which plays a major role in reducing the progression of symptoms occurred due to ADR's. The results of this study will provide baseline data about the age groups, Genders affected with different types of cancers and anatomical systems affected due to chemotherapeutic regimens. Within the shortest study period, we observed that there is highest incidence of ADR's associated with different Grades in subjects who are undergoing Chemotherapy. It was also identified that some patients couldn't attend early screening and were not early diagnosed due to the presence of barriers such as low economy, lack of awareness about the cancer and cultural inheritance; such patients were diagnosed with metastatic or late stages of cancer. Hence, these patients when exposed to highly potent drugs will be at a greater risk to develop ADR's. So, Improvement in Spontaneous reporting of ADR's in Oncology can be achieved through Awareness lectures using Audio-Visual means, brochures to patient population and they should be encouraged to report whenever they feel anything suspicious. Not only to the patients, education Lectures have to conduct on Causality assessment of ADR's using standard scales (CTCAE, WHO-UMC, NARANJO) to HCP's like Nurses, Clinical pharmacists, Residents, Interns. Till now, there is no clinical pharmacist in the Oncology, there is an urgent need to involve clinical pharmacist in such activities by the government not only to reduce ADR's but also to minimize Drug Related problems (DRP's).

LIMITATIONS

Due to the lack of time period we have done a study only on severity assessment of ADR's without including DRP's.

This study was limited to ADR's from Chemotherapeutic drugs and their combinations alone excluding the patients who exposed to ADR's because of Neo-Adjuvant therapy (Chemoradiation).

Large number of populations could have included in the study.

FUTURE DIRECTIONS

Studies related to DUR can be conducted.

Studies can be carried out on ADR's assessment specified to one particular type of cancer by including PK and PD characteristics.

epidemiological and pharmacoeconomic studies can be carried out.

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