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Assessment and Management Pattern of Chemotherapeutic Drug Induced Adverse Effects among Cancer Patients at Tertiary Care Centre

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Authors' contributions

This work was carried out in collaboration between all four authors. In this study author SMF designed the study proposal, conducted the study and involved in every stage of the study. Author KD involved in data collection and data refining of the study. Author JS involved in statistical analysis and literature searches in the study, and author SD reviewed and managed the analysis of the study and approved the final manuscript. Final Manuscript is finalized by all above author. All authors read and approved the final manuscript.

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ABSTRACT

Aim and Objective: Cancer chemotherapy drugs causes substantial toxicity and produces number of adverse effects which can significantly reduce patient's health related quality of life. The aim of this study was to perform the assessment and explore the management practice of chemotherapy induced side effects among cancer patients.
Material and Methods: Demographic characteristics of patient undergone cancer chemotherapy and adverse drug reactions (ADRs) of chemotherapeutic drugs were noted in patient's case report form. Assessments of ADRs were performed for Severity, Causality and Preventability of each ADR. Association between occurrence of severe ADRs and patient' characteristics were studied using chi square statistics. Frequencies of ameliorative therapy were studied in each patient.
Results: 120 patients were selected and included in the study and a total of 412 ADRs were detected after cancer chemotherapy. Majority (60%) of the participant were female. Most common

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cancer was found as breast cancer (23%). Commonly used chemotherapy regimens were combination of carboplatin and paclitaxel (14%). Upon severity assessment of ADR, more than one third categorized as "Severe" ADR (36.4%). Majority of the Severe ADR were alopecia and nausea & vomiting. Most of the ADRs (73%) on preventability assessment were found as Not-Preventable. There is a significant association between occurrence of severe ADRs and age, sex & chemotherapy regimen. Combination of palonosetron, dexamethasone and pantoprazole were used as ameliorative therapy (43.3%).

Conclusion: Cancer chemotherapy drugs produce numerous adverse effects. Assessment of severity of ADRs and associated triggering factor may support in management practice of side effects.

Keywords: Chemotherapy; causality assessment; ameliorative therapy.

1. INTRODUCTION

Cancer has been reported as one of the most common leading causes of death in the world [1]. In India, number of new cases of cancer and deaths due to cancer increased double-fold in last decades. Consumption of tobacco and increase in alcohol intake has been attributed to the risk factor for oral, oesophageal, larynx, and liver cancers in India [2]. Modernization and practice of unhealthy lifestyle which involves cigarette smoking, high fat, and low fibrous content diets are also majorly associated with higher incidence of cancer in developing countries [3]. The most common sites of cancer reported in India are the breast, lung, mouth, cervix, uterus, and tongue [4]. Therapeutic strategies for cancer are influenced by clinical characteristics of tumor-like signs and symptoms, stage, localization, and histological type. The most commonly used chemotherapeutic drugs are pyrimidine analogues (5-Fluorouracil (5-FU), Capecitabine), purine analogues (Mercaptopurine), and platinum compound (Cisplatin, Oxaliplatin). These drugs are having a narrow therapeutic index and show dose-related inter-individual effects due to their variation in metabolism [5]. Among all treatment modalities, chemotherapy still represents a center of pharmacological strategy for different types of solid cancer treatments and improves patient conditions [6]. The chemotherapeutic drug produces toxicity as an extension of their therapeutic action and may hamper the patient quality of life by producing numerous adverse effects [7].

Adverse Drug reaction (ADR) is an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of medicinal products. ADR is defined by World Health Organisation (WHO) as "any response to a drug, which is noxious, unintended and occurs at a doses used in man for prophylaxis, diagnosis or therapy" [8]. Among the anticancer drugs currently in use, the overall magnitude of ADRs, endured by oncology patients is high [9]. The most common adverse effect due to cancer chemotherapy is nausea, vomiting, alopecia, myelosuppression, cardiovascular toxicity, mucositis, hemorrhagic cystitis, and electrolyte imbalance [10]. Most of the patients receiving the antineoplastic treatment needed help to prevent and ameliorate adverse events (AEs) produced by them, and with the disease itself [11]. Due to the narrow therapeutic index of the antineoplastic drugs, early identification of adverse drug reactions helps in administering ameliorative therapy to counter their toxic effects [12]. Toxicity assessment in cancer chemotherapy patients needed special attention and more vigilance particularly in patients receiving the poly-chemotherapeutic drugs in the first few months, as it has a potential role in producing adverse effects [13]. It has been considered the need of current times to study the nature of ADRs produced by antineoplastic drugs for their proper management. Toxicity amelioration of some commonly associated ADRs is managed by primary care physicians; however, treatment of severe and rare ADRs needs to be explored. Therefore the aim of this study was planned to estimate the assessment and management practice of ADRs due to chemotherapeutic drugs observed in cancer patients in a tertiary care hospital.

2. MATERIAL AND METHODS

2.1 Data Collection and Study Protocol

Sample size for this study was calculated using proportion population formula. Assuming occurrence of at least one adverse effect due to cancer chemotherapy is 80%, relative error (d) 10% at 95% confidence interval, sample size came to 100. Considering 20% non responder or

loss to follow up, final sample size was 120. Patients being prescribed chemotherapy drug treatment for the first time attending or referred to the hospital were included in the study. Patients excluded from the study are having concurrent medical illnesses, overprescribing, accidental and deliberate overdosage, and a history of drug abuse and addiction. Data regarding the demographic profile, drugs used and ADRs produced were obtained from the patient and from their in-patient file, using standard case report form. Details of the diagnosis and concomitant drug have given and relevant biochemical parameters were also recorded confirmed by the treating physicians.

The severities of reported ADR were assessed using the "Modified Hartwig and Siegel" scale [14]. The causal relationship between suspected medication(s) and ADRs were assessed using the Naranjo's causality assessment scale [15]. According to the Naranjo's algorithm scale, Causality is defined on the basis of total score as “Definite reaction >9”, “Probable reaction 5-8”, “Possible reaction 1-4” and “Doubtful reaction 0” [15]. Preventability assessment of noted ADRs was done by using the "Schumock and Thronton" Scale. ADRs were classified as "Definitely Preventable", "Probably Preventable" and "Not Preventable" [16].

2.2 Statistical Analysis

Data entry, cleaning and analyses were done using SPSS (version 25) software. Descriptive statistics like proportion, frequency distribution were performed for patient demographic profile. Severity [14], Causality [15] and Preventability [16] of reported ADRs were studied. Pearson chi square test were used to evaluate association between occurrence of severity of ADRs and patients characteristics & preventability of ADRs.

3. RESULTS

3.1 Demographic Characteristics of Patients

A total of 120 samples were included in the study. The mean age of the total patient who participated in the study was 46.87 (Standard Deviation SD 10.1), the minimum age was found out to be 18 years and the maximum age was 75 years. 79(65.8%) patients were categorized in age 18-50 years. Out of 120 patient, gender female were 72(60%) and majority of patient 109(90.8%) were married. Frequencies of occupation were calculated. Most of the patient, 72(42.5%) were homemaker followed by 21(17.5%) laborers (Table1). Breast cancer 28(23%) was found to be the leading site in this study followed by gastric 19(15.8%), colorectal 16 (13.13%), ovarian15 (12.5%), lung 10(8.3%) and other carcinoma 25(20.8%). Details are described in Fig. 1.

Table 1. Demographic characteristics of patient (N=120)

Variables	Frequency (%)
Age (years	
18-50	79 (65.8)
51-<	41 (34.2)
Sex	
Female	72 (60)
Male	48 (40)
Marital status	
Married	109(90.8)
Unmarried	11 (9.2)
Religion	
Hindu	72 (60)
Muslim	48 (40)
Occupation	
Home-maker	51 (42.5)
Labour	21 (17.5)
Business	19 (15.8)
Job	13 (10.8)
Student	7 (5.8)
Elderly	5 (4.2)
Unemployed	4 (3.3)

3.2 Treatment Regimens and Adverse Effect Profile of Anticancer Drugs

The majority of the patient 98 (81.7%) received poly- chemotherapy as their treatment modalities. The most commonly administered chemotherapy regimen was a combination of Carboplatin & Paclitaxel 17(14.2%). Administration of Platinum compounds in form of cisplatin, carboplatin, and oxaliplatin, mono-therapy or in combination therapy accounts for more than sixty percent of patients who received anticancer medication (Table 2)..

A total of 412 chemotherapy-related ADRs were detected from 120 cancer patients. The most common ADR was found out to be nausea & vomiting 73 (17.7%) followed by alopecia and neutropenia (Fig. 2).

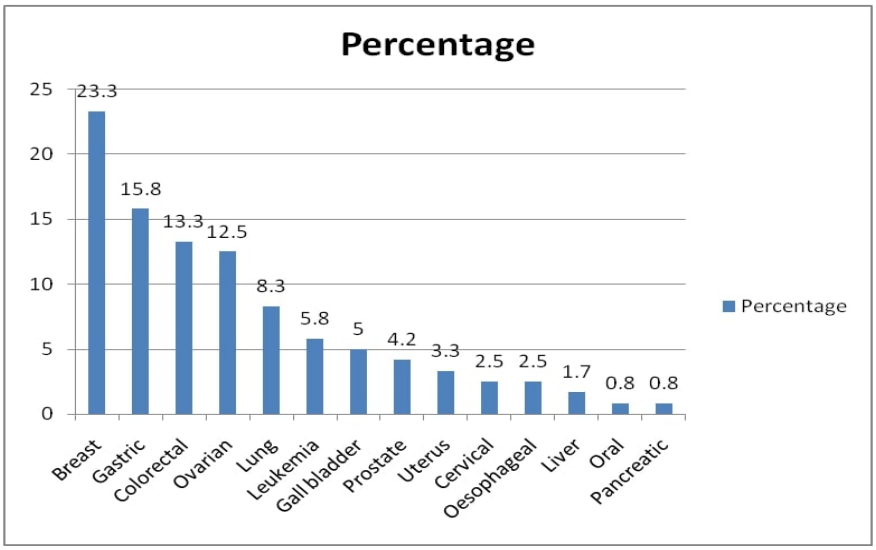

Fig. 1. Cancer types observed in this study

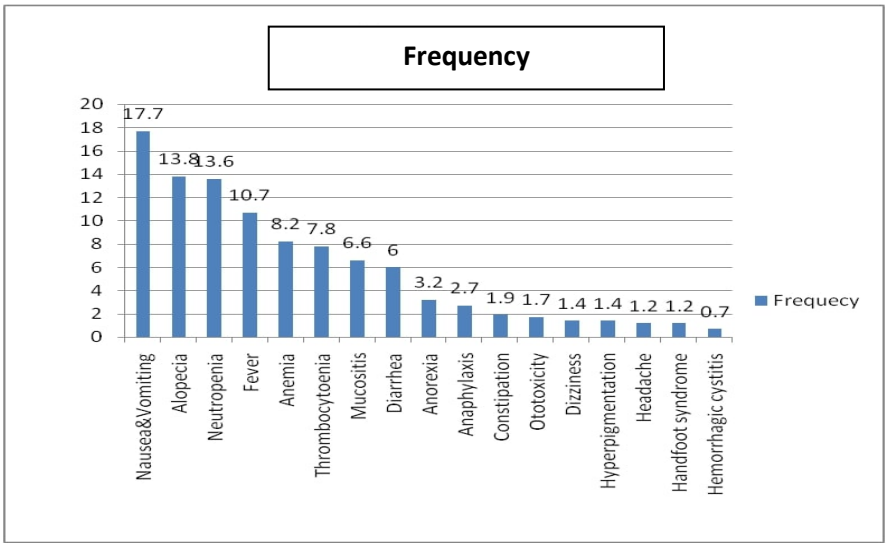

Fig. 2. Frequency of ADR induced by chemotherapy

Table 2. Chemotherapy regimen used in the study

Chemotherapy regimen	Patients(N=120)	Frequency (%)
Carboplatin+Paclitaxel	17	14.2
Cyclophosphamide+ Adriamycin+5-FU	16	13.3
Cisplatin+Paclitaxel	14	11.7
Cisplatin+5-FU	12	10
Cisplatin	11	9.2
5-FU+Leucovorin+ Oxaliplatin	8	6.7
Gemcitabine+Carboplatin	8	6.7
Paclitaxel+Trastuzumab	7	5.8
Oxaliplatin	4	3.3
Cyclophosphamide+ Mitomycin+5-FU	3	2.5

Chemotherapy regimen	Patients(N=120)	Frequency (%)
Cytrabine+Daunorubicin	3	2.5
5-FU+Leucovorin	3	2.5
Vincristine+Prednisone	3	2.5
Adriamycin	2	1.7
Gefitinib	2	1.7
Carboplatin	1	0.8
Cisplatin+Adriamycin+ Tamoxifen	1	0.8
Cytarabine	1	0.8
Epirubicin+Oxaliplatin	1	0.8
5-FU+Leucovorin+ Oxaliplatin	1	0.8
Gefitinib+Carboplatin	1	0.8
Paclitaxel	1	0.8

3.3 Assessment of ADRs Due to Cancer Chemotherapy

All ADRs (412) occurred in total 120 patients received chemotherapy drugs were assessed for severity, causality and preventability. Assessment of severity of the recorded ADRs were performed using modified Hartwig severity scale as "Mild", "Moderate" and "Severe". Maximum number of ADR 150(36.4%) was found to be “Severe” ADR. The Severe grade ADR observed mostly as alopecia (57%) followed by nausea & vomiting (35.6%) (Table 3). Causality assessment was done according to Naranjo's algorithmic scale. Out of 412, 281(68%) of the ADRs were analyzed as “Probable”. Alopecia (26.3%) noted as highest "Definite" ADR. (Fig. 3). Preventability assessment of all "Severe ADR" was performed by using the "Schumock and Thronton" Scale and it was found that 60% ADRs were “Not-Preventable” during the course of chemotherapy (Fig. 4).

3.4 Ameliorative Therapy for Management of Chemotherapy Induced ADRs

Different medications were used for toxicity amelioration in patients received chemotherapeutic drugs. Mostly patients 52(43.3%) administered palonosetron with dexamethasone and pantoprazole combination. Other most common combination noted for toxicity amelioration were the addition of folic acid and vitamin B complex 46(38.3%) (Table 4).

3.5 Factors Associated with the Severity of ADRs

Association of age group of the patients and severity of ADRs studied. A higher percentage (56.6%) of total ADR occurred in patients of 51< of age group. Out of which, 59.2% of ADRs were noted as "Mild & Moderate" and 40.8% were categorized as "Severe ADRs". While in age group 18-50, the Severe ADRs were comparably

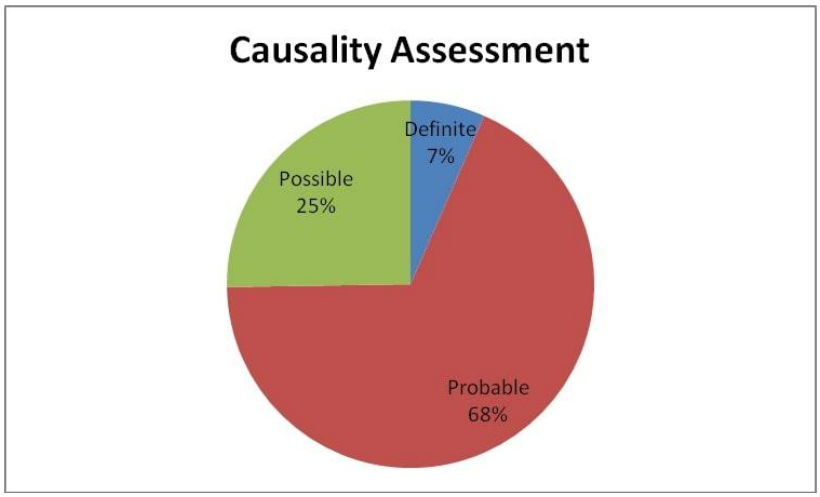

Fig. 3. Causality assessment (Naranjo's algorithmic scale)

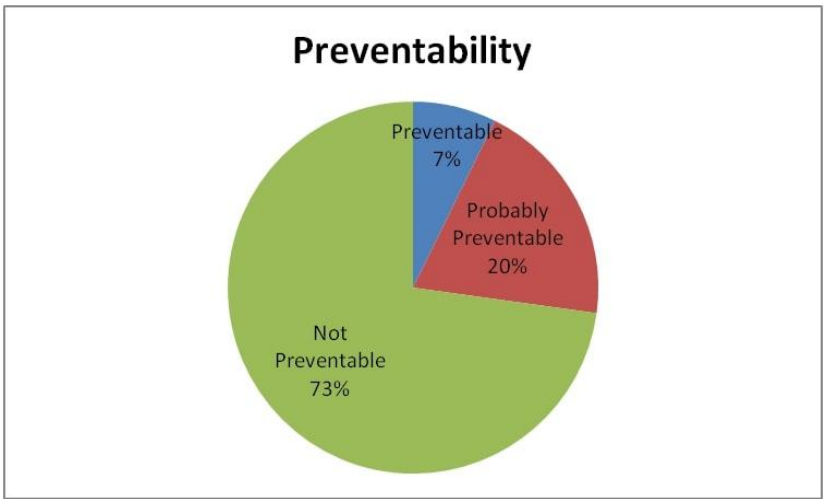

Fig. 4. Preventability assessment of Severe ADRs (Modified Schumock and Thronton criteria)

lower (30.7%). Association of gender and severity of ADR revealed that major (60%) ADRs observed in female patients. Occurrence of the "Severe ADR" reported in male patients was 27.9% while it was remarkably greater in female patients (42.1%). Patients who received mono-therapy was encountered "Severe ADRs" in less proportion (24.3%) as compare to those exposed to poly-therapy chemotherapeutic drugs (39%). On performing chi square analysis, there is a significant association between occurrence of Severe ADRs and age group, gender & chemotherapy regimen of the patients. Preventability of the ADRs is not statistically significant with the occurrence of Severe ADRs (Table 5).

4. DISCUSSION

Cancer chemotherapeutic drugs used to eradicate tumor cell; causes substantial toxicity and produce a number of adverse effect which is needed to treat promptly. The use of these agents must outweigh the risk over benefit [17]. Occasionally, ADRs produced by them are the limiting factor in finalizing the endpoints for treatment protocols because of their non-specificity and their potential to affect most of the rapidly proliferating cells of the body [9]. Some of the side effects caused by chemotherapy drugs have unpredictable onset and it is needed to identify earliest as they can be life-threatening and fatal [18].

Table 3. Assessment of ADRs for Severity (Modified Hartwig Scale)

Type of ADRs	Mild (%)	Moderate (%)	Severe(%)	Total (%)
Nausea&Vomiting	10 (13.7)	37(50.7)	26 (35.6)	73 (17.7)
Alopecia	0	0	57 (100)	57 (13.8)
Neutropenia	11 (19.6)	22 (39.3)	23(41)	56 (13.6)
Fever	27 (61.4)	8 (18.2)	9 (20.4)	44 (10.7)
Anemia	10 (29.4)	14 (41.2)	10(29.4)	34 (8.2)
Thrombocytopenia	7 (21.9)	12 (37.5)	13 (40.6)	32 (7.8)
Mucositis	8 (29.6)	14 (51.9)	5 (18.5)	27 (6.6)
Diarrhea	5 (20)	14 (56)	6 (24)	25 (6)
Anorexia	5 (38.5)	7 (53.8)	1 (7.7)	13 (3.2)
Anaphylaxis	11 (100)	0	0	11 (2.7)
Constipation	7 (87.5)	1 (12.5)	0	8 (1.9)
Ototoxicity	7 (100)	0	0	7 (1.7)
Dizziness	6 (100)	0	0	6 (1.4)
Hyperpigmentation	6 (100)	0	0	6 (1.4)
Headache	2 (40)	3 (60)	0	5 (1.2)
Handfoot syndrome	3 (60)	2 (40)	0	5 (1.2)
Hemorrhagic cystitis	1 (33.3)	2 (66.7)	0	3 (0.7)
Over all	**126 (30.6)**	**136 (33)**	**150 (36.4)**	**412 (100)**

Table 4. Ameliorative therapy used in patient receiving chemotherapeutic drugs

Ameliorative Thearpy	Frequency	Percentage
Palonosetron+ Dexamethasone+Pantoprazole	52	43.3
Palonosetron+ Dexamethasone+B-Complex+Folic Acid	46	38.3
Palonosetron+ Dexamethasone+B-Complex+Folic Acid+Mesna	7	5.8
Palonosetron+ Dexamethasone+B-Complex+Folic Acid+Filgrastim	5	4.2
Palonosetron+ Dexamethasone+B-Complex+Folic Acid+Levamisole	4	3.3
Palonosetron+ Dexamethasone+Pantoprazole+Loperamide	4	3.3
Palonosetron+ Dexamethasone+Pantoprazole+Diphenhydramine	1	0.8
Palonosetron+ Dexamethasone+B-Complex+Folic Acid+Amifostine	1	0.8
Total	**120**	**100**

Table 5. Association between cancer patient character and Severity of ADR produced

Variables	ADRs(%)	Mild & Moderate	Severe	*P*-Value
Age group				
18-50	179 (43.4)	124 (69.3)	55 (30.7)	
>51	233 (56.6)	138 (59.2)	95 (40.8)	.035
Sex				
Male	165 (40)	119 (72.1)	46 (27.9)	
Female	247 (60)	143 (57.9)	104 (42.1)	.003
Number of Chemotherapy				
Monochemotherapy	74 (18)	56 (75.7)	18 (24.3)	
Polychemotherapy	338 (82)	206 (91)	132 (39)	.017
Preventabiltity				
Preventable	112 (27.2)	77 (68.8)	35 (31.2)	
Not Preventable	300 (72.8)	185 (61.7)	115 (38.3)	.18

In this study, the majority of the participant 98(81.7%) were on the poly-chemotherapy. Mostly ADRs 338(82%) occurred in patients who received poly-chemotherapy as their treatment modalities. Upon severity assessment using modified Hartwig scale, a total of 132(39%) ADRs were noted as Severe ADR. There is a significant association between the occurrence of Severe ADRs and chemotherapy regimens (p=0.017). This study corroborates with other studies as poly-pharmacy in current times are more common pattern of chemotherapeutic drug use in elderly patients as compared to younger patients, it could also play a risk factor for more in number and severe ADRs [19]. Patients on poly-chemotherapy are more prone to experience ADRs and drug-drug interaction [20].

Most common ADR found in our study were nausea and vomiting. It is also reported by some other studies which states nausea and vomiting are one of the most common chemotherapy induced ADR and classified as acute, delayed or anticipatory [21]. The severity of nausea and vomiting depends on the types of specific chemotherapy regimen [22]. In this study most common regimen was carboplatin and paclitaxel combination. Other platinum compounds used as chemotherapy were cisplatin and oxaliplatin as mono-therapy or in combination with others. It could be the reason for higher incidence of ADRs in poly-chemotherapy group and also for nausea &vomiting as most common ADR.

The use of corticosteroids with other antiemetic agent has a very prominent role in preventing delayed emesis [23]. To manage chemotherapy-induced nausea and vomiting (CINV) three-drug regimens are advocated prior to chemotherapy; 5 Hydroxytryptamine-3 (5HT3) receptor antagonist in combination with dexamethasone and Neurokinin-1 receptor antagonist (NK1) such as aprepitant [24]. The higher incidence of CINV in our study may be due to cost and unavailability of the aprepitant one of the important drugs recommended to treat CINV, however, most of the patients received dexamethasone for toxicity amelioration.

The next most common ADR associated with chemotherapy reported in this study are alopecia, neutropenia, fever, anemia and thrombocytopenia. Alopecia is very common in patients receiving doxorubicin and cyclophosphamide in their chemotherapy regimen. Temporary vasoconstriction can be

used to reduce blood circulation in scalp to prevent hair loss [25]. Our study participants received various combinations of doxorubicin for chemotherapy (Table 2). Neutropenia is also reported as one of the most common chemotherapy-related adverse effects [26]. In this study, a total of 13.6 % ADRs were neutropenia, out of which 41% were assessed as severe ADR. Filgrastim a synthetic drug were used to prevent neutropenia in a total of 4.6% of patients in this study. Other studies also reported using Granulocyte-Colony Stimulating Factor (G-CSF) and Granulocyte-macrophage colony Stimulating factor (GM-CSF) to increase the White Blood Count (WBC) [27,28].

Our study shows the occurrence of mucositis (6.6%) and diarrhea (6%) as the fifth ADR observed after hematological toxicity. For their management, diphenhydramine and loperamide were used respectively (Table4). Chemotherapeutic drugs may cause mucositis and diarrhea by damaging rapidly dividing cells of the gastrointestinal tract [29]. Oral mucositis can be prevented by using chlorhexidine mouth wash at bedtime prophylactically. The addition of xylocaine, diphenhydramine and vitamin E as ameliorative therapy is also beneficial [30]. The most common chemotherapy drugs causes diarrhea are 5-Flurouracil (5-FU) and methotrexate. It can be controlled by adding diphenoxylate with scopolamine combination or by using loperamide [31].

In this study, we observed that age group 18-50 years patient produces 30.7% as “Severe” ADR, while patients fall in age group >51 produces 40.8% as "Severe" ADRs. There is a significant association between occurrence of Severe ADRs and age group (p=0.035). Another study also suggests that aged cancer patients are using more than two drugs for their treatment is having chances of double risk of adverse effects. Ageing and co-morbidities increase the chances of non-compliance and non-adherence to therapy especially in elderly and pediatric patients [32].

In our study 60% of the total ADRs were noted in the female patients, they mostly experienced "Severe" ADRs (42.1%) which is closed to the finding of another study. There is a significant association between the occurrence of Severe ADRs and gender was found (p=0.003). The severity of ADRs reported in female were significantly higher, it's maybe due to the alteration in hormonal activity at different stages of life [33].

Preventability assessment of ADRs explains that 60% of ADRs were "Not Preventable" while 29% and 11% ADRs were designated as "Probably Preventable" and "Preventable" respectively. However, the association between the occurrence of Severe ADRs and Preventability is not statistically significant. A report from one study regarding Preventability pattern of chemotherapy induced ADRs were comparable to our study [34].

5. CONCLUSION

This study explained the demographic pattern of patients who received cancer chemotherapy drugs. The majority of ADRs occurred due to chemotherapeutic drugs are noted in female patients. Breast cancer was found to be the most common cancer among all. The most common ADRs due to cancer chemotherapy were nausea & vomiting followed by alopecia and neutropenia. All ADRs produced due to cancer chemotherapy were assessed for severity, causality assessment, and preventability. There is a statistically significant association found between the occurrence of Severe ADRs and age group, gender & chemotherapy regimen. The pattern of ameliorative therapy used in each patient after chemotherapy cycles were studied. Association of ADRs and patient characteristics reveals that the need of more attention towards detection of chemotherapy-induced ADRs and the use of ameliorative therapy. By understanding the nature of ADRs, proper selection and use of drugs can be advocated for the prevention of toxicity for each ADR. Further studies for particular strategies in managing different ADRs with a holistic approach may attribute to improve the safety of patients.

CONSENT

Written informed consents were taken regarding their willingness for participation in the study and they were told that their participation in the study is voluntary and informed that they can withdraw from the study at any point of time. Detail explanations of the study and its objectives were given to study subjects. Subjects were assured anonymity and confidentiality of data given by them.

ETHICAL APPROVAL

All authors hereby declare that study is approved by the Institutional Ethical Committee of the

institution. IEC-SU/2017/1226(5) and have therefore been performed in accordance with the ethical standards. Origin and conduct of this study was Department of Pharmacology, Santosh Medical College and its associated university hospital, Santosh University, Ghaziabad (NCR), India.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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