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ADVERSE DRUG REACTIONS TO CANCER CHEMOTHERAPY IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Aim: The aim of this study was to identify and evaluate the adverse drug reactions due to the anticancer drugs in patients with malignancy. **Objective**: The objective of this study was to evaluate the clinical course of drug reaction and to assess the causality and preventability of the identified adverse drug reaction. **Methodology**: This is a prospective observational study conducted over a period of one year in 200 patients receiving cancer chemotherapy in the medicine, surgery, pediatrics and gynaecology wards of goa medical college. **Results**: The number of females were 147 (73.5%) and the number of males were 53 (26.5%).The total number of adverse drug reactions observed were 656. Approximately 63% of the adverse drug reactions were classified as probable according to Naranjo algorithm with a score ranging from 5-8 while 37% were categorised as possible with score of 1-4. Assessment of the severity of the adverse drug reactions was done by Hartwig Seigel scale with 95% of the ADRs belonging to mild category. Majority of the cancers were of breast i.e 77 out of 200 patients (38.5%). Among the chemotherapeutic drugs used 26% were antimetabolites. The most common adverse effect observed was haematological in 85% of patients. Next adverse reaction noticed was nausea/vomiting forming 17% of total and alopecia formed 39% of ADR's. **Conclusion**: For safety and increased efficacy of the drugs pharmacovigilance is of utmost importance in the department of oncology. It helps to increase the compliance of the patient, decrease the incidence of the ADRs and decrease the financial burden for the patient and the society.

KEYWORDS: Adverse drug reactions, cancer chemotherapy, pharmacovigilance.

INTRODUCTION

An adverse drug reaction (ADR) is defined by World health organisation (WHO) as "Any response to a drug which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy." Worldwide ADRs were responsible for 10% of hospital admissions[1] and 6% of hospitalised patients suffer from ADRs.[2]

The chemotherapy drug regimens are very complicated and patients with cancer have a low threshold for tolerance. The drugs used in the management of cancer have very narrow therapeutic window.[3] ADRs are commonly seen in patients receiving chemotherapy and they are most of the times predictable and preventable.[4] At times the ADRs are very severe and the expense incurred to treat them is more than the cost of treatment of the disease itself. The therapeutic action not only affects the tumour cells but also the healthy rapidly dividing cells of the body.[5]

Adverse drug reactions cause human suffering and also increase the healthcare costs and hence create a major clinical issue.[6] It is associated with a marked increase in the length of stay in the hospital, increased cost and risk of death. India has a low rate of ADR reporting which can be due to low level of awareness among healthcare professionals about ADR monitoring and pharmacovigilance.

Pharmacovigilance is "the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems. Recently its concern has been widened to include herbals, traditional and complementary medicines, blood products, biological, medical devices and vaccines." (WHO 2002). This programme helps in the early detection and management (if necessary) of the unwanted drug effects.

ADRs can be reported by yellow card system. It is cost effective and ensures safety in the usage of the drugs.[7] Health care providers can do spontaneous reporting of the ADRs. The pharmacy and lab databases are frequently used.[8] When used alone, they are not effective in increasing the rate of ADR reporting. There is not a single perfect method for ADR detection. The

various available sources should be used simultaneously. This will help to increase the knowledge of impact of the hospital ADR.[9]

AIMS AND OBJECTIVES

1. To identify and evaluate the adverse drug reactions due to the anti-cancer drugs.
2. To study the clinical course of drug reaction.
3. To assess the causality, preventability and management of the identified ADR.

MATERIALS AND METHODS

This study was conducted in the wards of Surgery, Gynaecology, Paediatrics and Medicine departments of Goa Medical College, Bambolim Goa, with the approval of the Institutional ethics committee. Study included patients diagnosed with cancer and treated with chemotherapeutic drugs. The duration of the study is of 1 year.

Patient Selection

Patients diagnosed as having a carcinoma using clinical and histological methods were included in the study. Only patients who were admitted in the ward were included.

Inclusion Criteria

Patients of either gender, irrespective of age and receiving cancer chemotherapy were included in the study.

Exclusion Criteria

1. Patients receiving only radiotherapy.
2. Patients receiving chemotherapy for conditions other than carcinoma were not included in the study.

Study Design

This study is a prospective observational study of patients receiving chemotherapy for cancer. A detailed history, including the medication history was taken and physical examination was done. The laboratory results were analysed and a proper history of the illness was taken. Naranjo algorithm was used as a standard to do the causality assessment. The hartwig seigel scale was used to assess the severity of the reactions.The preventability of the ADRs was analysed using modified Shumock Thornton criteria.

RESULTS

1. Demographic Characteristics

Among the 200 patients in this study the number of females were 147 (73.5%), while the number of males were 53 (26.5%)(Fig. 1).According to the age distribution of the patients the majority of the cases having adverse drug effects belonged to the age group of 50-59 years (Fig.2).

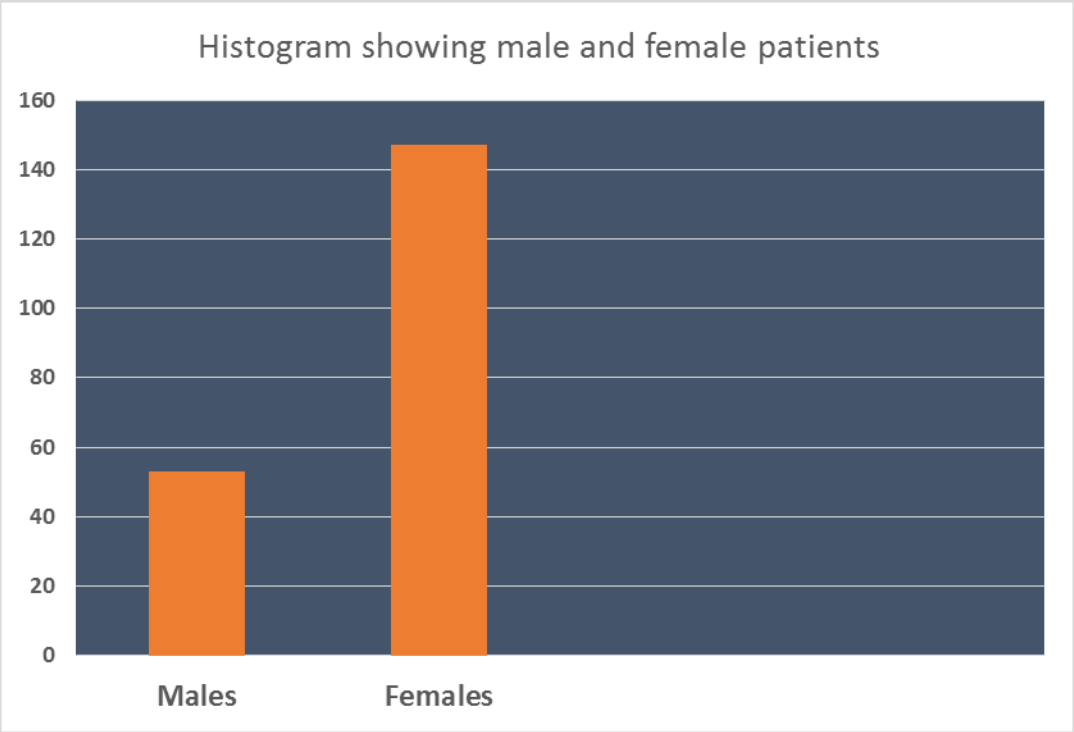

Figure 1: Graph showing female and male patients distribution in the study.

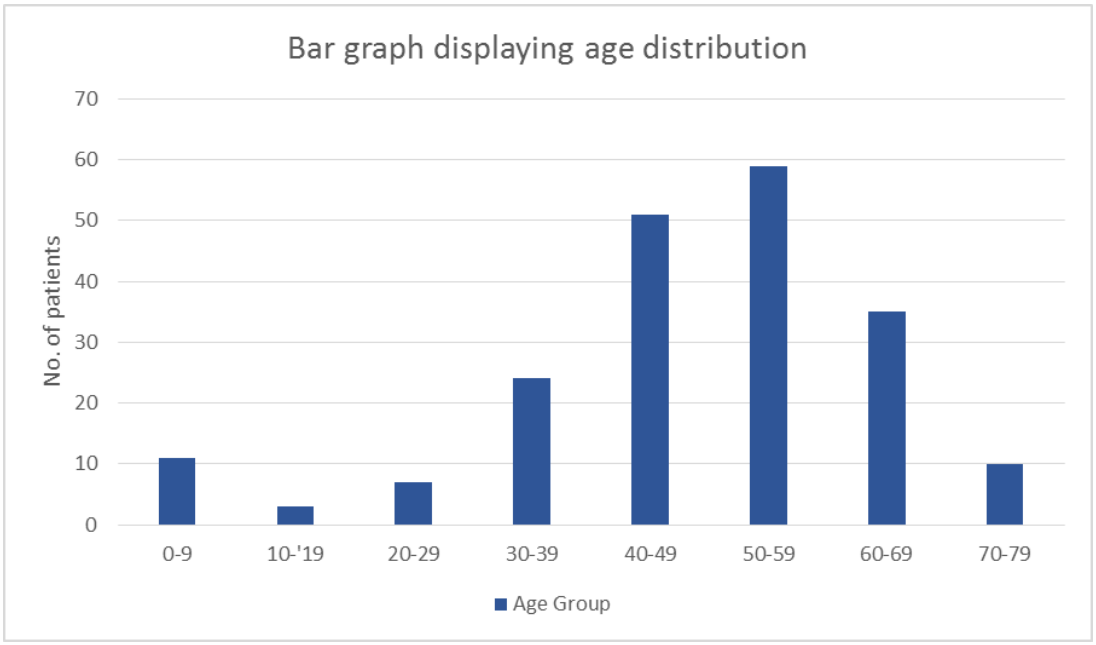

Figure 2: Bar graph showing the age distribution of patients.

2. Type of Cancer

Majority of the cancers were of breast i.e 77 out of 200 patients (38.5%). The next common cancer encountered was of the gastrointestinal tract. These included colon cancer, ca stomach, cancer of the rectum and one patient with malignancy of the pancreas. Oral cavity cancers included malignancy of the tongue and buccal mucosa also. Haematological malignancies such as AML, ALL, CLL were observed in 14% of the total patients which was 28 cases. The lymphoid malignancies such as Hodgkin's and non-Hodgkin's lymphoma were also included in this category. The other cases which formed 3% of the population included carcinoma of testis, rhabdomyosarcoma etc. (Fig.3)

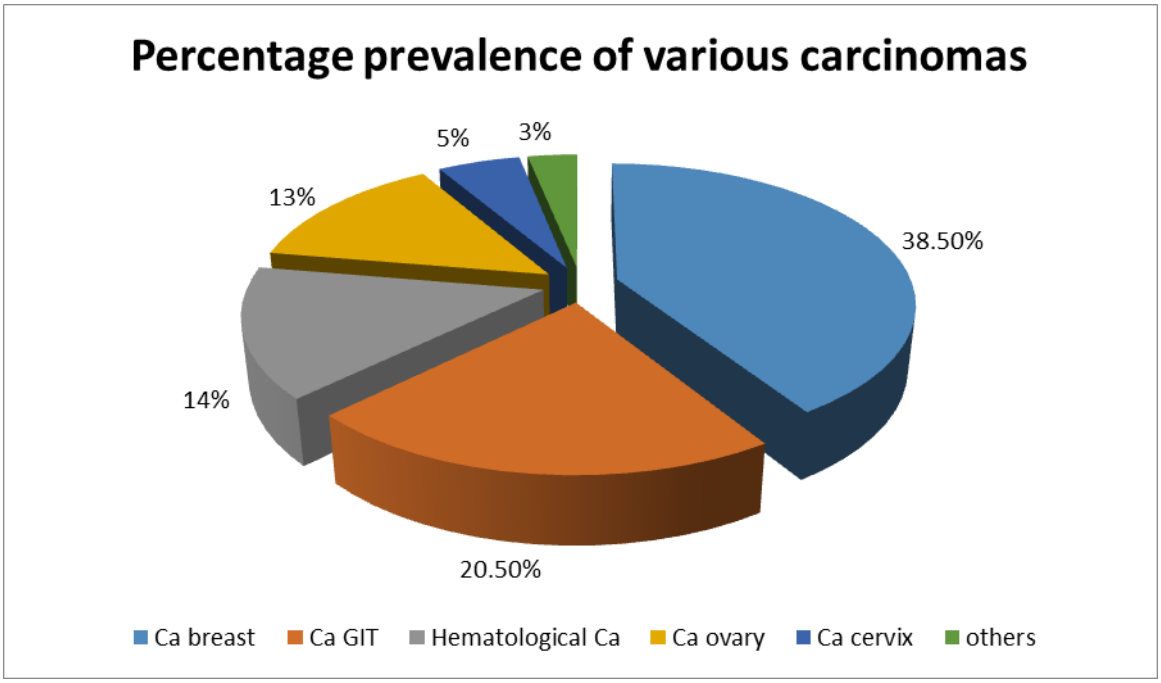

Figure 3: Pie chart showing percentage of various carcinomas observed in the Study.

3. Type of chemotherapy (Fig. 4)

Among the chemotherapeutic drugs used 26% were antimetabolites among which 5FU is the most common. Other antimetabolites used are capacitabine, cytarabine, methotrexate and 6 mercaptopurine in the descending order of use. The use of alkylating agents was 19% among the total drugs used which included cyclophosphamide, ifosphamide, dacarbazine and bendamustine in decreasing order of use. Anticancer antibiotics in the cancer chemotherapy include epirubicin, doxorubicin,

bleomycin, daunorubicin and actinomycin formed 19% of the total chemotherapeutic drugs. Natural products formed 17% of the drugs on the charts of chemotherapy patients. Most commonly used natural products are docetaxel, vincristine, vinblastine and etoposide. Targeted chemotherapy which includes Bortezomib, imatinib and antibodies like trastuzumab and rituximab formed 5% of the drugs. The platinum based compounds (cisplatin, carboplatin, oxaliplatin) formed13% of the total cancer treatment. The miscellaneous drug asparaginase was given in 4 patients.

The adjuvant chemotherapy formed the mainstay of the treatment which accounted for 96% of the patients while chemotherapy alone was given in 4% of the patients.

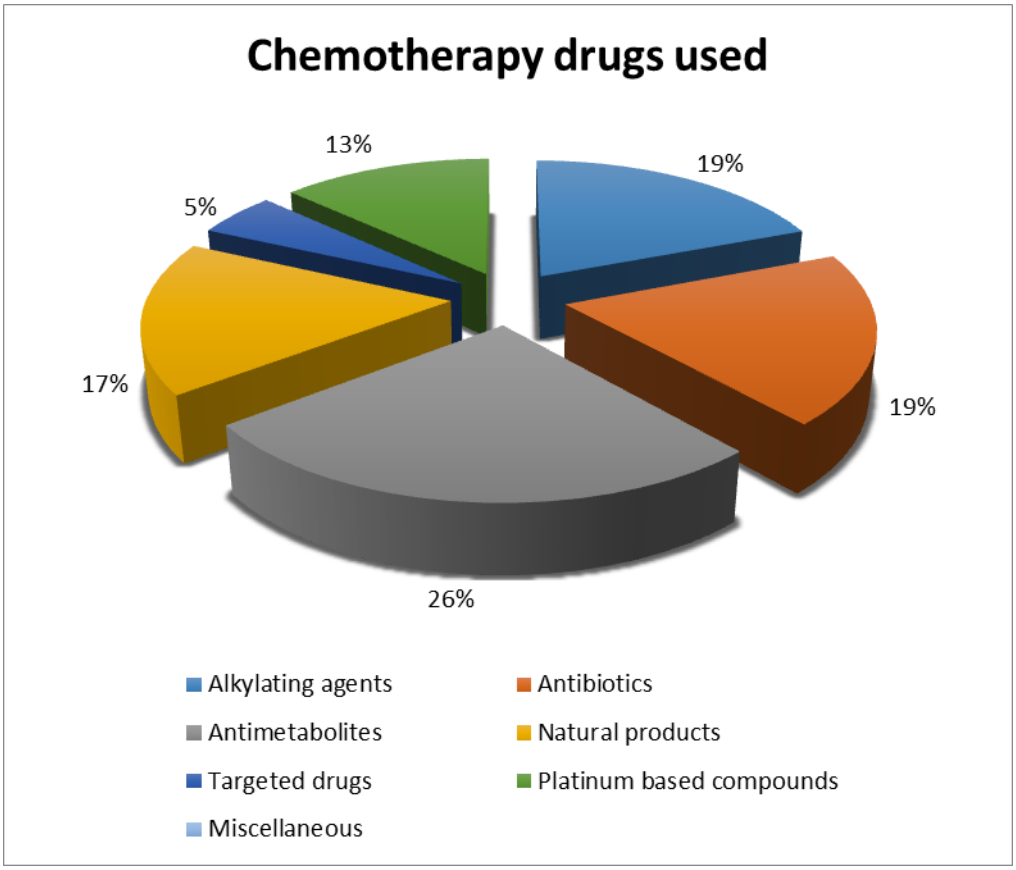

Figure 4: Pie chart showing various chemotherapy drugs used.

4. Prevalence of ADR's in various age groups

The major number of adverse effects occurred in the age group of 50-59 years which formed 29.5% of the total study population. The percentage prevalence of patients gradually increased forming a peak at the age group of 50-59 years and then had a decline. (Table 1)

Table 1: Percentage prevalence of adverse drug reactions according to the age group.

Age group	Percentage of ADRs
0-9	5%
10-19	1.5%
20-24	4.5%
30-39	13%
40-49	26%
50-59	29%
60-69	17%
70-79	4%

5. Type of adverse drug reactions. (Fig.5)(Table 2)

Nausea or vomiting was the most common adverse effect observed in 17% of patients. It was more in patients receiving platinum based compounds as part of the chemotherapy especially cisplatin. The next adverse reaction noticed was alopecia which formed 12% of total number of adverse drug reactions. However the patients suffering from total baldness was fewer. This adverse reaction was noticed more in patients with the CEF regimen.

The most common haematological adverse drug reaction was normocytic normochromic anemia(12%) followed by neutropenia (11.4%)and thrombocytopenia in (1.5%). Except in one patient of thrombocytopenia the reactions were not severe which warranted change or discontinuation of treatment or any intervention.

Peripheral neuropathy consisted of 4% of all ADRs. The various symptoms and signs detected in the patients with peripheral neuropathy were decreased sensation of crude

touch and fine touch, tingling numbness, decreased temperature perception and burning in the upper or/and lower limbs.

Skin and nail discolouration formed 4% of the ADRs. 24.5% of the patient's sufferd from diarrhoea or constipation which made it 7.4 % of the total number of ADRs. Hepatotoxicity was observed in 2 patients. This was in the form of hepatic sinusoidal reaction and increased hepatic transaminases. There was no death among the patients in this study.

Some of the adverse drug reactions noticed in the study are: hand foot syndrome due to capecitabine, peripheral neuropathy to paclitaxel, mouth ulcers due to 5FU, darkening of nails due to cyclophosphamide and hepatic sinusoidal syndrome due to Actinomycin D.

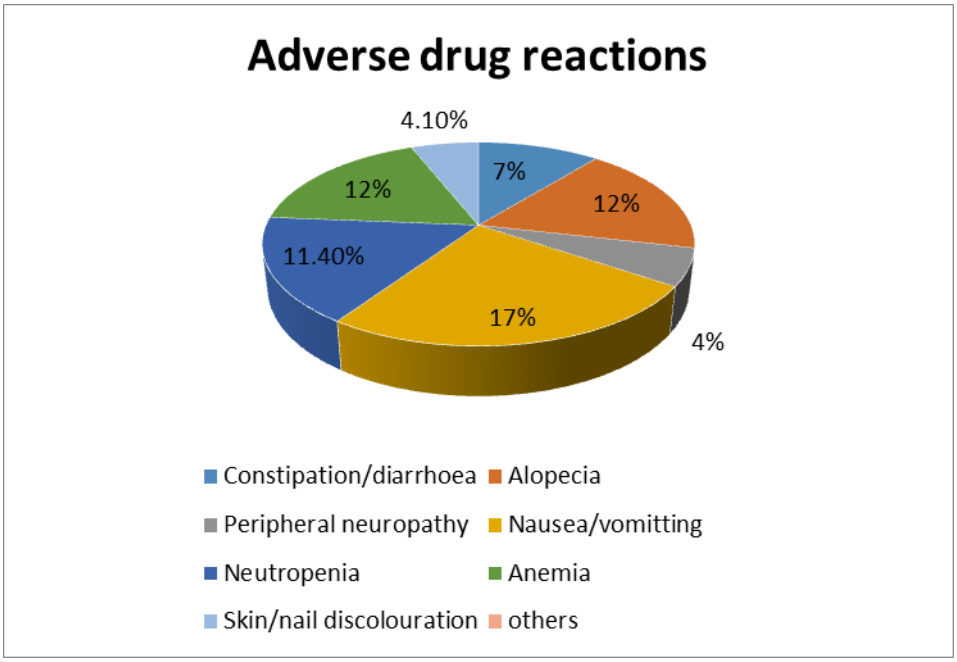

Figure 5: Pie chart showing various adverse drug reactions in percentage.

Table 2: Number of patients and different adverse effects.

Adverse effects	Number of Patients
Constipation/diarrhoea	49
Alopecia	78
Peripheral neuropathy	25
Nausea & vomiting	112
Neutropenia	75
Normocytic normochromic anemia	79
Skin/nail discolouration	27
Thrombophlebitis	3
Hepatotoxicity	2
Thrombocytopenia	10

Approximately 63 percent of the adverse drug reactions were classified as PROBABLE according to Naranjo algorithm with a score ranging from 5-8 while 37 percent were categorised as POSSIBLE with score of 1-4.

The severity of the adverse drug reactions was assessed using Hartweig Seigel scale. Most of the ADRs that is 95% belonged to the mild (level 1) i.e the ADR require no change in the treatment with the suspected drug. Around 4% of the ADRs belonged to Moderate category (level 3) i.e an antidote or other treatment is required with no increase in the length of the stay. One ADR i.e hepatic sinusoidal syndrome was categorised as Severe(level5).

The preventability of the ADRs was analysed using modified Shumock Thornton criteria. 27.2% of the ADRs were definitely preventable, 42% were probably preventable and 30.7% were not preventable.

DISCUSSION

According to this study there is an increase in the prevalence of patients suffering from breast cancer in this region. It is stipulated that the increase in the incidence of breast cancer in India could be due to various factors such as adoption of a more westernised lifestyle with resulting changes in the diet, physical activity and fertility.[10] Early menarche is also an important risk factor which causes an increased exposure of females to estrogen in their lifetime. This is similar to a study conducted by Mugada et al.[11]

In this study the incidence of ADRs was found to be greater in female participants as compared with male participants. The findings of this study are similar to a study done by Poddar et. Al.[4] This can be due to the fact that the incidence of breast cancer is on a rise in India

and globally as stated earlier. The age group most commonly presenting with ADRs in this study was the elderly age group i.e 50-59 years. This is similar to a study by Poddar et al[4] in which ADRs were found to be also more in the elderly older age group. This can be due to a decreasing excretory capacity and a lower drug metabolism in the elderly which leads to accumulation of drugs and an increase in the severity and incidence of ADRs.[12]

The most common ADR in this study was nausea and vomiting which formed 17% of the total number of ADRs. This was similar to that observed by Rout et al (17.37%).[13] There is stimulation of the chemoreceptor trigger zone situated in the area postrema in the medulla oblongata. This area is not bound by the blood brain barrier. Hence emetogenic chemicals can reach through the cerebrospinal fluid or blood.

The next most common adverse effect observed was alopecia which was 12% of the total ADRs. This is similar to a study conducted by Mallik et al[14] who had alopecia as 14.3% among the total ADRs. The alopecia influences the body image and self-esteem of the patient in a negative manner. Almost 8% of patients refuse chemotherapy due to fear of hair loss. The drugs primarily act on the keratin producing cells of the matrix and damage them.[15]

The next adverse effect encountered in this study was haematological in which normocytic, normochromic anaemia formed 12% of total ADRs, neutropenia formed 11.4% and thrombocytopenia formed 1.5%. The anemia seen is multifactorial. The malignancy leads to anemia as there is infiltration of the bone marrow by the cancer cells. Neutropenia was seen in 75 of the patients in this study. The cause of the neutropenia is similar to anemia. The cancer cells infiltrate the bone marrow and affect the progenitor cells of the white cell lineage. This affects all the white cell subtypes. This can in turn result in infections due to decreased immunity.[12]

Diarrhoea formed 1.6% of the total ADRs and Constipation formed 5.7%. The diarrhoea and constipation is less than that observed by Chopra et al[16] (7.1%) and Wahlang et al[5] (12.26%) respectively. The drugs most commonly causing diarrhoea are 5 fluorouracil, capacitabine and irinotecan. The exact cause is not known but maybe due to damage to the intestinal villi and enterocytes. Constipation affects majority of the chemotherapy patients yet it is an underestimated adverse effect. It hampers the quality of life and can also lead to serious bowel obstruction. There is very little research available on chemotherapy induced constipation. It is implicated to be mainly due to damage of the enteric nervous system.[17]

Peripheral neuropathy in the form of tingling or numbness formed 4% of the total number of ADRs. The peripheral neuropathy was observed in spite of administration of vitamin B12 supplementation. Paclitaxel caused the classical “glove and stocking” neuropathy. Platinum containing compounds like carboplatin caused hand foot syndrome. These target the various structures of the neurons like myelin sheath, cell body, axons etc.[18]

Hepatotoxicity was seen in 3 patients. One patient presented with sinusoidal obstruction syndrome due to vincristine in this study. The hepatotoxicity normally is caused due to the active metabolites generated in the phase I reactions which in turn alter the function of mitochondria and cause immunological damage.[19] The 8 year old child with sinusoidal obstruction syndrome presented with abdominal pain, fever and raised liver function tests, 5 days after the administration of vincristine for Wilms tumor.

The naranjo algorithm was used to assess the probability of the adverse drug reactions. Out of the total ADRs 63% were categorised as probable and 37% were categorized as possible. This is in contrast to that observed by Chopra et al[16] who reported 80% as possible and 20% as probable and similar to Mugada et al[11] who classified 76% as probable and 20% as possible.

According to Hartwig Siegel severity scale, 95% of the ADRs belonged to the mild category (level 1), 4% to the moderate category (level 3) and 1% to the severe category (level 5). This is similar to a study by Wahlang et al.[5]

According to modified Shumock Thornton scale, 27.2% of the ADRs were definitely preventable, 42% were probably preventable and 30.7% were not preventable. A study done by Rout et al[13] found preventable ADRs to be 64.45% while that by Hema et al[20] classified 14.7% of the ADRs as not preventable. All the patients with ADRs were managed symptomatically. There was no death due to ADR reported in this study.

The ADRs not preventable included peripheral neuropathy, skin pigmentation and alopecia. Nausea or vomiting can be probably prevented by increasing the dose and frequency of the antiemetic or by changing it to a one with higher efficacy. The definitely preventable ones are neutropenia and anemia which can be prevented by giving appropriate supplements.

The management for some of the ADRs in this study were done by prophylactically giving certain drugs like ondansetron or aprepitant and dexamethasone for vomiting, vitamin B12 for peripheral neuropathy and colony stimulating factors for anemia and neutropenia in few patients.

CONCLUSION

For safety and increased efficacy of the drugs pharmacovigilance is of utmost importance in the department of oncology. It helps to increase the

compliance of the patient, decrease the incidence of the ADRs and decrease the financial burden for the patient and the society. This study showed that monitoring of ADRs is possible in the hospital setting and this will improve the quality of treatment and patient care. There is an increased need to create awareness and train the health care providers. This will ensure early diagnosis and treatment of the adverse event. In the interest of public health, increased reporting nationally will lead to better reporting globally.

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