African Journal of Pharmaceutical Research & Development

Vol. 8 No. 2; pp. 100-107 (2016)

PATTERN OF ADVERSE DRUG REACTIONS OF ANTICANCER DRUGS IN ONCOLOGY UNIT OF A TERTIARY CARE TEACHING HOSPITAL IN SOUTH WEST, NIGERIA

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ABSTRACT

The work was aimed at studying the pattern of ADRs due to chemotherapeutic agents with specific objective to assess the causality, severity and management of these reactions in a tertiary care hospital, South West Nigeria. This was a retrospective descriptive study. Medical records of patients were studied with patient details, adverse drug reactions (ADR) and medications used to manage the reactions recorded using the designed ADR data collection form. The ADRs were assessed for causality and severity using the Naranjo and Hartwig assessment scales respectively. A total of 433 ADRs were recorded from 170 patients of which 96 (56.47%) were females and 74 (43.53%) were males. Most common cancers encountered were breast (25.30%), colorectal (21.20%), cervical (10.00%) and prostate (10.00%). Nausea/vomiting (21.50%) accounted for the most ADRs followed by alopecia (17.10%). Antimetabolites (28.00%) and platinum compounds (24.00%) were the most implicated drug classes causing ADRs. Naranjo causality assessment scale showed (66.48%) of the reactions to be "possible" and (33.52%) to be "probable" while the Hartwig severity assessment scale revealed majority of the reactions to be "moderate" (63.50%), followed by "mild" (35.11%) and "severe" (1.39%). Medications commonly prescribed for the management of the reactions were ondansetron, proton pump inhibitors, dexamethasone, chlorpheniramine and metoclopramide. The study revealed high incidence of ADRs with chemotherapeutic agents. The prevalence of ADRs was considerably high in spite of the use of existing premedications. Most of the ADRs were found not reported using the pharmacovigilance system, leading to under reporting. As such, health care givers should be educated to look out for such, with emphasis to employ strategies to prevent, minimize and manage ADRs of cytotoxics with peculiar side effects. The knowledge will serve to prevent similar reactions in the future by rational and judicious use of preventive measures to decrease human suffering and economic burden to the patients and society.

KEYWORDS: *Adverse Drug Reactions (ADRs), Chemotherapy, Causality, Pharmacovigilance*

INTRODUCTION

Adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, therapy of disease or for the modification of physiological function [1]. About 2.9 – 5.6% of all hospital admissions are due to adverse drug reactions [2]. Unfortunately, awareness of ADRs and its surveillance are inadequate with few reports available in developing countries like Nigeria [3, 4].

The aim of causality assessment is to state how certain one can be, that the suspected ADR is actually as a result of the administered drug [5]. Several scales were used to assess causality e.g. WHO scale, European ABO system and Naranjo Scale. Naranjo ADR scale is the most widely employed. It categorizes ADRs into: Definite, Probable, Possible and Doubtful [5, 6]. The Hart wig

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severity scale is used to classify severity of ADR into mild, moderate and severe [7].

The burden of cancer continues to rise globally largely because of increasing older population and more adoption of carcinogenic attitudes such as smoking [8]. According to the World Health Organization (WHO), about 7.4 million cancer-related deaths (13.00% of all deaths) occurred in 2013 and the figure is projected to continue rising, with an estimation of 11.5 million deaths by 2030 [8, 9].

Chemotherapeutic drugs have a narrow therapeutic window and the dosage needed to achieve a therapeutic response is mostly toxic to the body's rapidly proliferating cells [10]. The tissues mostly affected by these drugs are those which are rapidly dividing such as the bone marrow, gastrointestinal tract and hair follicles [11].

The scarcity of studies relating to drug safety monitoring in Nigeria was the motivation behind the present study which was aimed at evaluating the pattern of ADRs occurring in cancer patients treated with chemotherapy in a tertiary care hospital in South West, Nigeria. The study will serve to improve the care of cancer chemotherapeutics patients.

The primary objectives of the study include:

- To determine the demographic prevalence of the cancers in LUTH
- To study the occurrence of suspected ADR with anticancer agents in LUTH.
- To assess the causality and severity of the ADRs using the Naranjo ADR causality assessment scale and Hart wig severity scale respectively
- To determine the premedication used in the management of the ADRs.

MATERIALS AND METHODS

This retrospective, descriptive, case record study was conducted after obtaining the approval of the Lagos University Teaching Hospital (LUTH) Health Research and Ethics Committee (ADM/DCST/HREC/APP/546). Comprehensive medical records were collected and subsequently studied for adverse drug reactions. A modified Nigeria National Pharmacovigilance Centre (NPC) form for reporting of suspected ADRs was used for data capture. A total of 170 patients receiving chemotherapy who developed ADRs were included in the study. Details such as the diagnosis, demography, administered medications, adverse drug reactions and premedications used in the management of the ADRs were carefully recorded. Males and females of all ages diagnosed with cancer and undergoing chemotherapy that developed at least, one ADR during the treatment period were included. The recorded ADRs were assessed for causality using the Naranjo algorithm, while the severity of the reported reactions were assessed using the modified Hartwig scale. The data collected were coded using Microsoft excel and analyzed with the help of SPSS software version 20.0. The results were analyzed using descriptive statistical analysis and represented in frequencies, percentages, tables, pie chart and bar charts.

RESULTS

Among the 170 patients included in the study, 56.47% who developed ADRs due to cancer chemotherapy were females while 43.53% were males. Further analysis revealed that 65.80% of the patients were married while 34.13% were singles. The prevalence of cancers was found to be most common in the age group 51 – 60 years (29.40%), followed by 61 – above (24.70%). The least incidence was observed between the age group of 11 – 20 years (2.35%).

CLINICAL DIAGNOSIS

The six common type of cancers seen were breast (25.30%), colorectal (21.20%), cervical (10.00%), prostate (10.00%), lung (7.05%) and ovarian (5.30%). Gender based analysis showed the most frequent cancers in females to be breast (44.80%), cervical (17.70%) and ovarian (9.38%), while that in males were colorectal (41.90%), prostate (23.00%) and lung (10.80%).

DISCUSSIONS

The International Agency for Research on Cancer (2013 data) states that about 102,079 new cancer cases are discovered annually with about 71,571 deaths in Nigeria. A study by Jinichi et al [10] at the Institute of Medical Science, University of Tokyo showed a high prevalence of adverse drug reactions in cytotoxic drugs. In this study, of the 170 patients studied, 56.47% were females while 43.53% were males. These findings were similar to a study carried out in a cancer research institute in Meldova, Italy by Tenti et al [12] who reported 57.40% females and 42.60% males, but in contrast to similar findings in a Teaching Hospital in Gujarat India by Yash et al [13] who observed higher incidences in males 54.29% compared to females 45.71%. Some reasons for these differences can be hormonally related, e.g. meningioma which is more common in females because the tumor has estrogen and progestin receptors [14]. Many more differences are

due to the behavioral pattern of the sexes as more women are historically more overweight while males have a higher incidence of smoking (more lung cancer) and higher alcohol consumption (more liver cancer) [15].

The prevalence of different cancers revealed that patients are mostly affected by breast cancer (25.30%). This finding is similar to the study by Amartya [16] from the Oncology Unit of an Urban Multispecialty Hospital in India. Amartya [16] also showed the 2nd, 3rd, 4th and 5th most frequent cancers to be lung, ovary, cervical and rectal respectively. This is slightly different from our study that showed the prevalence rate to be colorectal (21.20%), cervical (10.00%), prostate (10.00%) and lung (7.05%) cancers in similar categories above.

Sub-classification based on gender from our work, revealed the three most common cancers in females to be breast (44.80%), cervical (17.70%) and ovarian (9.38%), while colorectal cancer (41.90%), prostate cancer (23.00%) and lung cancer (10.80%) were the cancers most seen in males. This finding is closely related to the study by Kirthi et al [17] in a Tertiary Hospital in Hydrabad who reported frequency of cancers in females to be breast (40.00%), cervical (11.40%) and ovarian (8.60%) while cancers in males were lung (10.00%), bladder (8.30%) and NHL (8.30%).

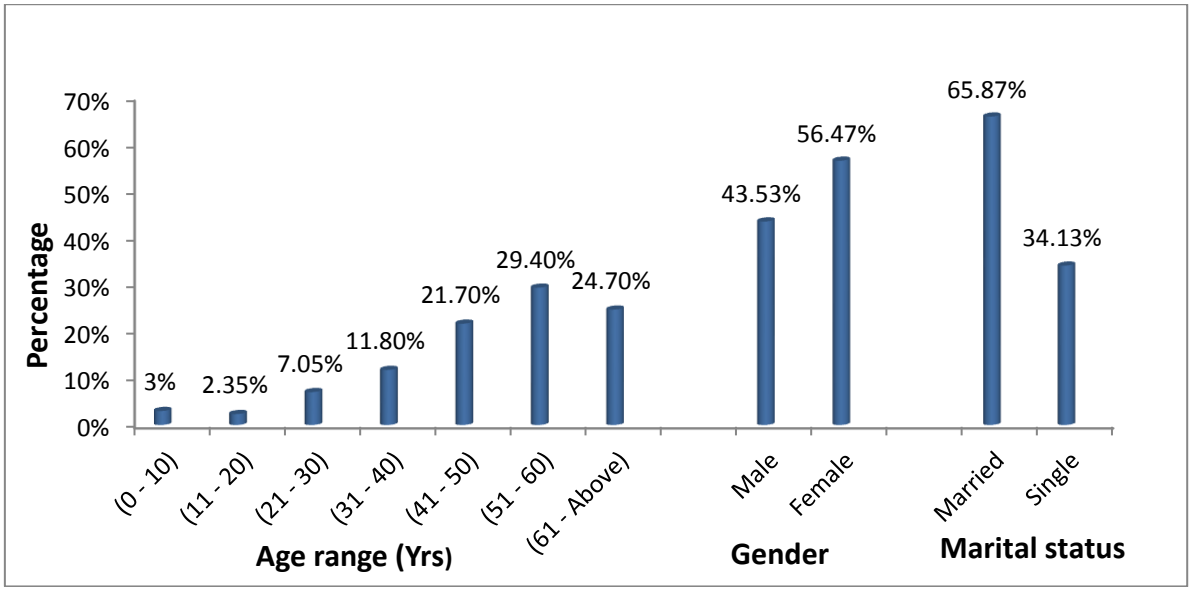

Figure 1: Demographic prevalence of cancer patients in LUTH

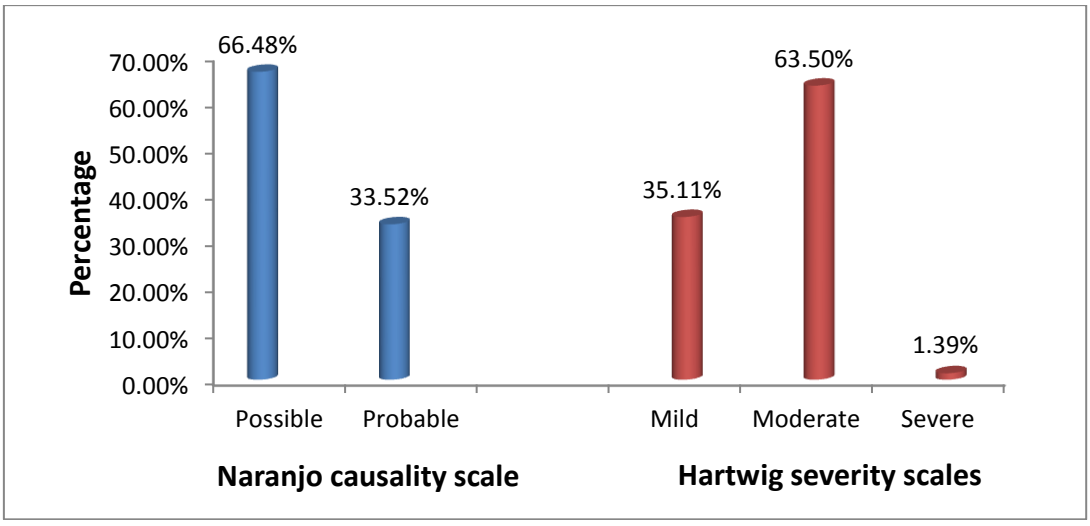

Figure 2: Causality and severity distribution of recorded ADRs

Table 1: Frequency of prescription and recorded ADR for each drug

Type of malignancy		No. of Prescriptions (%)	No. of ADR (%)
1.	5-Fluorouracil	59(16.80)	82(18.90)
2.	Cisplatin	43(12.20)	69(15.90)
3.	Cyclophosphamide	36(10.20)	49(11.30)
4.	Doxorubicin	40(11.40)	39(9.00)
5.	Paclitaxel	32(9.10)	36(8.30)
6.	Oxaliplatin	33(9.40)	31(7.16)
7.	Docetaxel	21(5.97)	26(6.00)
8.	Gemcitabine	23(6.54)	24(5.64)
9.	Carboplatin	08(2.27)	15(3.46)
10.	Capecitabine	11(3.13)	14(3.23)
11.	Vincristine	11(3.13)	10(2.37)
12.	Goserelin	07(1.99)	09(2.08)
13.	Epirubicin	08(2.27)	08(1.85)
14.	Bicalutamide	05(1.42)	06(1.36)
15.	Methotrexate	06(1.72)	05(1.15)
16.	Etoposide	03(0.85)	03(0.69)
17.	Cytarabine	01(0.28)	03(0.69)
18.	Tamoxifen	02(0.57)	02(0.46)
19.	Anastrazole	01(0.28)	02(0.46)
20.	Estramustine	01(0.28)	--
21.	Idarubicin	01(0.28)	--
	TOTAL	**352(100)**	**433(100)**

Table 2: Frequency of adverse drug reactions

Type of ADR		Count	Percentage (%)
1.	Nausea and Vomiting	93	21.50
2.	Alopecia	74	17.10
3.	Other GI symptoms	69	15.80
4.	Skin rash/Pruritus	37	8.45
5.	Oral mucositis	31	7.16
6.	Constipation	26	6.00
7.	Diarrhoea	18	4.16
8.	Nausea	11	2.54
9.	Leukopenia	10	2.21
10.	Anaemia	09	2.08
11.	Anorexia	08	1.84
12.	Nail discolouration	07	1.62
13.	Fever	06	1.39
14.	Neutropenia	04	0.92
15.	Headache	04	0.92
16.	Tinnitus	04	0.92
17.	Hypotension	04	0.92
18.	Insomnia	03	0.69
19.	Dyspnoea	03	0.69
20.	Hiccups	02	0.46
21.	Eye irritation	02	0.46
22.	Myalgia	02	0.46
23.	Dermatitis	02	0.46
24.	Numbness on nails	02	0.46
25.	Gyanaecomastia	01	0.23
26.	Thrombocytopenia	01	0.23
27.	Ototoxicity	01	0.23
28.	Erythema	01	0.23
29.	Peripheral neuropathy	01	0.23
30.	Maculopapular rash	01	0.23
	TOTAL	**433**	**100**

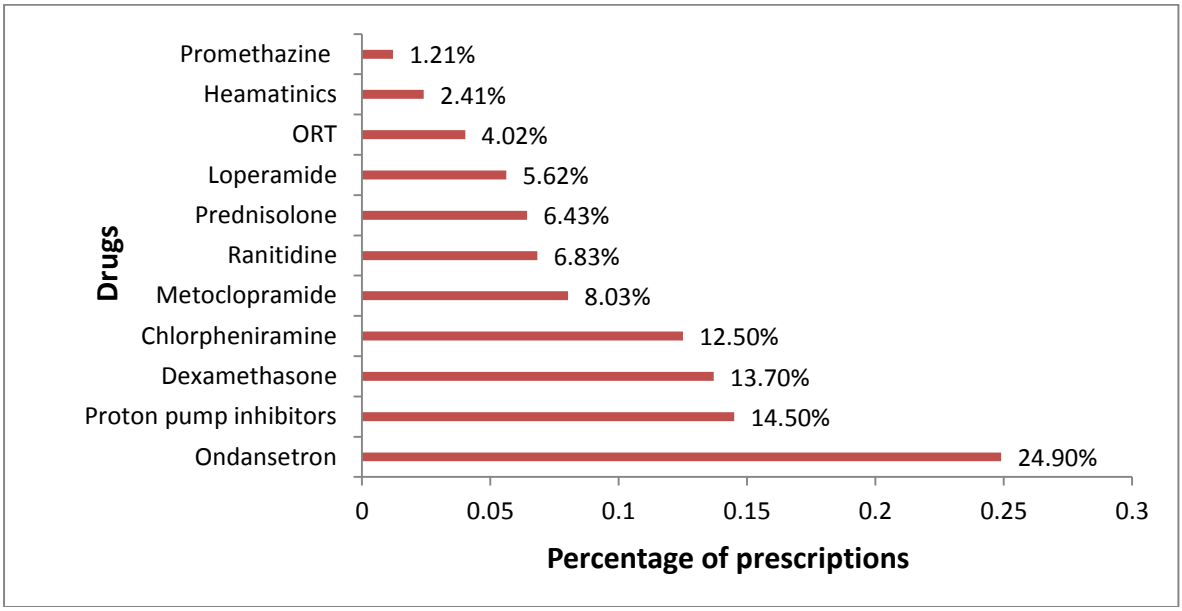

Figure 3: Medications used in the management of the ADRs

Table 3: Chi-Square Tests

NARANJO		Value	df	Asymp. Sig. (2-sided)
Probable	Pearson Chi-Square	289.414[b]	104	.000
	Likelihood Ratio	109.769	104	.330
	Linear-by-Linear Association	4.220	1	.040
	N of Valid Cases	57		
Possible	Pearson Chi-Square	1011.987[c]	360	.000
	Likelihood Ratio	398.246	360	.080
	Linear-by-Linear Association	3.246	1	.072
	N of Valid Cases	363		
Total	Pearson Chi-Square	1152.738[a]	450	.000
	Likelihood Ratio	540.070	450	.002
	Linear-by-Linear Association	9.519	1	.002
	N of Valid Cases	420		

Table 4: Chi-Square Tests

HARTWIG		Value	Df	Asymp. Sig. (2-sided)
Mild	Pearson Chi-Square	367.219[b]	156	.000
	Likelihood Ratio	172.409	156	.175
	Linear-by-Linear Association	.211	1	.646
	N of Valid Cases	129		
Moderate	Pearson Chi-Square	910.768[c]	340	.000
	Likelihood Ratio	368.650	340	.137
	Linear-by-Linear Association	10.682	1	.001
	N of Valid Cases	284		
Severe	Pearson Chi-Square	21.000[d]	12	.050
	Likelihood Ratio	16.152	12	.184
	Linear-by-Linear Association	.064	1	.800
	N of Valid Cases	7		
Total	Pearson Chi-Square	1152.738[a]	450	.000
	Likelihood Ratio	540.070	450	.002
	Linear-by-Linear Association	9.519	1	.002
	N of Valid Cases	420		

Our investigation showed that 5-Fluorouracil accounted for the most prescriptions (16.80%) and suspected ADRs (18.90%). This was followed by cisplatin with 15.90% ADRs and 12.20% prescriptions. Cyclophosphamide had 10.20% prescriptions and 11.30% ADRs, while doxorubicin

had 11.40% prescriptions and ADRs of 9.00%. The study by Tenti et al [12] in an Oncology Pharmacy unit in Meldova, Italy showed the five most frequent ADRs causing agents to be paclitaxel (19.90%), oxaliplatin (16.10%), carboplatin (14.00%), fluorouracil (11.20%) and gemcitabine (10.00%) respectively.

A further observation from our study based on the type of therapeutic regimen employed showed the FLOX regimen (5FU/Oxaliplatin) to account for the greater number of prescriptions (14.70%) and ADRs (15.00%). This is similar to the findings by Marilia et al [11] from the State University of Campinas in Brazil who observed the FLOX regimen to be (22.50%). Subsequent breakdown from our study gives out the next regimen with the most ADRs to be the FAC regimen (5FU/Doxorubicin/Cyclophosphamide) which has ADRs of 10.20% and 15.00% prescriptions.

Analysis of the encountered reactions showed nausea and vomiting (21.50%) to be the most prevalent ADR followed by alopecia (17.10%). Lakshmi et al [18] from the Department of Pharmacy, Chalapati Institute of Pharmaceutical Sciences reported alopecia (95.00%) and nausea/vomiting (82.00%) to be the two most occurring ADRs.

Initially, the majority of patients undergoing chemotherapy were expected to develop alopecia. However, although alopecia was the second most commonly encountered ADR in our study, its manifestation occurred in less than half of the patients (43.50%) which was lower than the stated value by Trueb [19] who estimated the incidence of alopecia in chemotherapy to be (65.00%). The lower figure observed maybe as a result of higher prescriptions of 5-fluorouracil and oxaliplatin which have been shown to induce lower proportions of alopecia [19].

From the study other GI symptoms (15.80%), skin rash/pruritus (8.45%) and oral mucositis (7.16%) occurred as the 3rd, 4th and 5th most common ADRs respectively, whereas Lakshmi [18] reported myelosuppression (42.00%), skin pigmentation (15.30%) and Itching (11.40%) in similar order. Constipation and diarrhoea also occurred at frequencies of 6.00% and 4.16% respectively. Most GI symptoms including mucositis are due to the effect of chemotherapy on rapidly proliferating cells. Diarrhoea occurs because the epithelial cells of the GIT are destroyed by certain antineoplastic agents that promote poor digestion and absorption of nutrients [11].

Causality status was assessed using the Naranjo adverse drug reaction probability scale where 66.48% of the reported ADRs had causality rating of "Possible" while 33.52% were termed "Probable". No reaction was found to be doubtful or definite. This finding is closely related to the study by Sharma et al [20] who got "possible" 65.40% and "probable" 34.40%. Proving causality beyond Probable is a challenging and multi-disciplinary task because several drugs which in most cases have similar tendencies to cause same reactions are used together. Furthermore, there is the need to determine plasma concentration of the drug [21]. Unfortunately, Therapeutic Drug Monitoring (TDM) is not common in the studied center.

Based on the Hart wig severity scale 63.50% of the ADRs were found to be "Moderate", 35.11% were "Mild" while 1.39% were "Severe". This pattern is closely related to what was reported by Gunaseelan et al [22] from the Department of Pharmacology Regional Institute of Tropical Science Manipul who observed severity to be "Moderate" (74.10%), "Mild" (17.90%) and "Severe" (8.00%).

Adverse drug reactions were also observed to have occurred more in female gender (65.50%) compared to males (34.50%). Another study by Kirthi et al [17] reported ADRs in both genders to occur in similar frequencies. However, increase in female gender from our study group in addition to higher cancer prevalence and higher prescriptions may also be due to the established facts that female patient are known to have 1.5 to 1.7 fold greater risk of developing ADRs compared to male patients [23]. The reasons for the increased risk are attributed to gender-related differences in immunological factors, hormonal factors, and pharmacokinetic factors [23].

The majority of the encountered adverse events was managed or premanaged using therapeutic interventions. Anticancer agents such as cisplatin and cyclophosphamide are highly emetogenic, but the use of antiemetics especially the newer classes have significantly decreased the morbidity associated with chemotherapy-induced nausea and vomiting [24]. About 249 intervention prescriptions were recorded. The most commonly prescribed antiemetics from the study were ondansetron (24.90%), dexamethasone (13.70%) and metoclopromide (8.03%). This was different from what was obtained by Lakshmi et al [18] who reported metoclopramide (87.00%), followed by ondansetron (25.10%). Gastrointestinal symptoms such as heartburn, dyspepsia, abdominal pain, flatulence etc. were managed mostly by proton pump inhibitors (14.50%) and ranitidine (6.83%).

Anti-histamines such as chlorpheniramine (12.50%) were also significantly used to counter skin rash/pruritus and other allergic cases. Loperamide (5.62%) with or without Oral Rehydration Therapy (4.02%) were frequently prescribed for disturbing cases of diarrhoea while those with anaemia were given haematinics (2.41%) except in few cases were blood transfusion was administered.

Limitations discovered during the study were the inability to monitor suspected ADRs serially because of the retrospective nature of the study and lack of scope for patients recall. Therapeutic drug monitoring was also not a common practice at the center. The short duration of the study also makes it difficult to detect chronic or delayed ADRs.

CONCLUSION

The study showed high prevalence of ADRs with the use of cancer chemotherapeutic agents. 5FU and Cisplatin were found to be responsible for the most ADRs. Early detection of these ADRs will enable the modification of doses, use of antidotes or substituting the offending agent(s) to minimize the damage. Most of the ADRs were found not reported using the pharmacovigilance system, leading to under reporting. Additionally, it was observed that medications mainly prescribed for adverse drug reactions tackle emesis and other gastrointestinal problems. However, there is very low probability that other ADRs like hemorrhagic cystitis from cyclophosphamide, cardio and nephrotoxicity from antitumor antibiotics such as doxorubicin and cisplatin or tumor lysis syndrome due to cytotoxics did not occur in the subjects. This suggests that, either there was low index of suspicion by health care givers to identify the aforesaid or lack of knowledge about these ADRs. As such, health care givers should be educated to look out for such, with emphasis to employ strategies to prevent, minimize and manage ADRs of cytotoxics with peculiar side effects. The knowledge will serve to prevent similar reactions in the future by rational and judicious use of preventive measures to decrease human suffering and economic burden to the patients and society.

AKNOWLEDGEMENTS

Our appreciation goes to the staff of Pharmacy and Record Department of LUTH Oncology unit for their patients and assistance in the course of the study.

AUTHOR DISCLOSURE STATEMENT

No conflict of interests exist in conducting and reporting of this work

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