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Original Research Article

Prospective observational study to evaluate the pattern of adverse drug events in cancer patients receiving anti-cancer agents in a tertiary care hospital

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ABSTRACT

Background: Adverse drug reactions (ADRs) associated with the use of anticancer drugs are a worldwide problem and cannot be overlooked. They range from nausea, vomiting or any other mild reaction to severe myelosuppression. The study was planned to evaluate the pattern of adverse drug events to anti-cancer agents in a tertiary care hospital.
Methods: This observational prospective study was carried out in a tertiary care hospital from 1st January 2011 to 31st December 2011. A total of 213 patients who fulfilled the inclusion criteria were enrolled in the study. Out of them, 8 patients were withdrawn from the study as they subsequently underwent radiotherapy. The adverse events observed during the treatment were noted and analyzed by using applicable statistics.
Results: Out of 205 patients, 98 were males and 107 were females. Breast cancer was the commonest type of cancer evident. A total 523 anti-cancer drugs were prescribed for the patients with alkylating agents being the most common. 635 adverse events (ADRs) were observed in patients with vomiting and nausea as the most common adverse drug reactions (ADREs). Majority of the ADRs (89%) had a latent onset (occurring 2 or more days after exposure to the drug). Few events were serious in nature (9%); fatal events were uncommon (0.31%). WHO causality was 'possible' for 94% of the events. ADRs were more frequently observed in females in the age group of 46-60 years; mood swings were significantly higher in women, while vomiting was found to be significantly common in men.
Conclusions: The study showed that chemotherapy has a high potential to cause ADRs. Thus, there is a need for vigilant ADR monitoring to prevent morbidity and mortality due to ADRs.

Keywords: ADRs, Cancer, Chemotherapy, Pharmacovigilance

INTRODUCTION

The prevalence of adverse drug reactions (ADRs) of anticancer drugs in Indian context is 10-12%.[1] Cancer is one of the leading causes of death worldwide with estimated 12% deaths annually.[2] In India the incidence of cancer is about 70-90 per 100 000 persons. Anticancer drug therapies are more prone to cause ADRs as these agents are cytotoxic and can damage the normally dividing cells along with the cancerous cells. Another reason of more ADRs in patient receiving anticancer drugs is that such patients receive multiple drugs making them more vulnerable to ADRs.[3,4]

Gender and age related risk factors also play an important role in the development ADRs. Chemotherapy induced nausea and vomiting is one of the most significant and common ADRs observed.[5] Apart from the known ADRs, some rare adverse drug events (ADEs) have also been identified for already established drugs. Nail pigmentation for cyclophosphamide, photolichenoid eruption for docetaxel, pancreatitis (Imatinib), panic attacks (Ifosfamide) and Capecitabine induced oral pigmentation and hand-foot syndrome.[3,6-9]

There is a dearth of ADRs data associated with chemotherapy drugs in countries like India and a systematic pharmacovigilance study on cancer chemotherapy has not been previously done in our setup.

So, a prospective observational study was planned to evaluate the pattern of adverse drug events to anti-cancer agents in a tertiary care hospital.

METHODS

This observational prospective study was conducted in the oncology set up of department of surgery in a large teaching based tertiary care hospital of over 1000 beds during the period of 12 months from 1st January 2011 to 31st December 2011. Approval of the Institutional Ethics Committee was sought before commencing the study.

Patients of both genders and age above 18 years, those diagnosed to have cancer by histological, radiological and various clinical methods and prescribed anti-cancer drugs and who are either on treatment or newly started on treatment were included in the study.

Patients who have ever received radiotherapy and who are not willing to give written informed consent were excluded from the study. Patients who subsequently underwent radiotherapy after enrollment were withdrawn from the study.

During the study period, anti-cancer regimens were noted and patients were interviewed for the occurrence of ADRs in the presence of their healthcare team i.e. nurses or doctors during every cycle. Patients were also provided with a diary to record the details of the ADRs as they occurred. During the patient interview- patient information, drug information, past medical history, laboratory investigations (hematology and biochemistry) were assessed during every chemotherapy cycle.

Suspected ADRs were analyzed for various parameters. The onset was classified as acute, sub-acute and latent.[10] The seriousness was evaluated as per WHO-UMC criteria into serious and not serious.[11] Severity of the adverse event was evaluated by modified Hartwig Siegel scale.[12] Causality was evaluated as per World Health Organization – Uppsala Monitoring Centre causality assessment scale.[13] All reported ADRs were studied in detail to understand the characteristics of ADRs based on patients' gender, age, onset, drugs involved in causing ADR, various organ system affected, predisposing factors, management and outcome of ADRs.

Statistical analysis

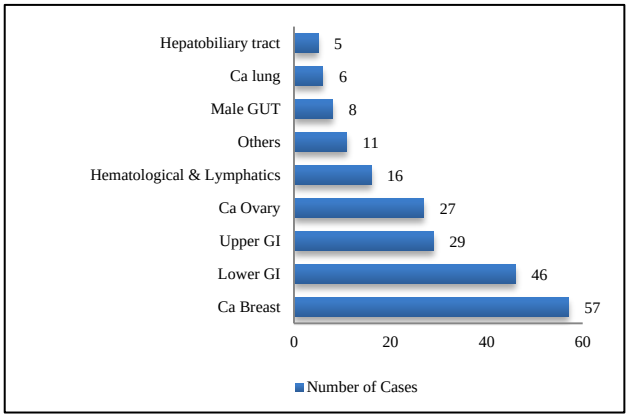
The effect of gender as risk factor for individual adverse events was evaluated using Pearson chi square test. The association between age and individual adverse event was evaluated by using one-way ANOVA test. All other results have been expressed in percentage frequencies.

RESULTS

During the study period, a total of 213 patients were enrolled in the study. Out of them, 8 patients were withdrawn from the study as they subsequently underwent radiotherapy. The data analysis pertains to 635 records of adverse drug events of 205 patients who were receiving anti-cancer drugs.

Table 1: Age and gender characteristics of the study population.

Gender Age (in years)	Male (N = 98)	Female (N = 107)	Total (N = 205)
18 to 30	14	11	25
31 to 45	27	33	60
46 to 60	40	45	85
> 60	16	18	34



GI: gastrointestinal; GUT: Genitourinary tract

Figure 1: Disease profile (type/site of malignancy) of the study population (N = 205).

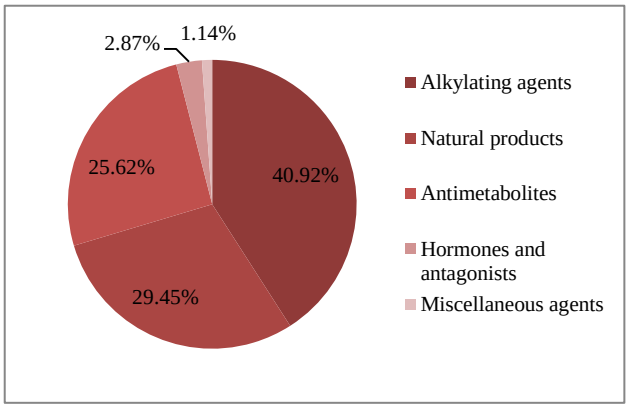


Figure 2: Classes of anti-cancer drugs prescribed in study population (n=523).

Table 1 shows the distribution of age and gender involved in the study. Out the 205 patients, 98 were males while 107 were females. Majority patients (41%) were under the age group of 46-60 years. Most common type was breast cancer (28%) followed by tumours of lower gastrointestinal tract (GIT), upper GIT, ovarian, lymphatic, male genitourinary tract (GUT) cancers as shown in Figure 1. In this study a total 523 anti-cancer

drugs were prescribed for 205 cancer patients as given in Figure 2. Of them, most common drugs prescribed were alkylating agents (40.92%).

Table 2: Profile of ADEs encountered in the study population with the frequency of individual events (N = 205).

Event	Frequency
Vomiting	79
Alopecia	73
Hyperpigmentation	61
Anorexia	59
Nausea	57
Diarrhea	32
Leucopenia	26
Paresthesia	20
Headache	19
Stomatitis	19
Anemia	16
Dizziness	16
Constipation	15
Myalgia/Arthralgia	13
Nail changes	13
Inj. site Induration/ulcer/wound infections	11
Dysgeusia	9
Significant weight loss	9
Insomnia	8
Heartburn	8
Mood changes	8
Thrombocytopenia	7
Abdominal pain/cramps	6
Malaise	6
Oligo/amenorrhea	5
Dysphagia	5
Fever with/without chills	5
Redness/dryness of eyes	4
Anastomotic leak	3
Flatulence/ bloating	3
Joint stiffness	3
Respiratory infections	3
Tremors	3
Convulsions	2
Pruritis	2
Ascites	1
Blindness	1
Cellulitis	1
Diminished vision	1
Disorientation	1
Thrombophlebitis	1
Trismus	1
Total	**635**

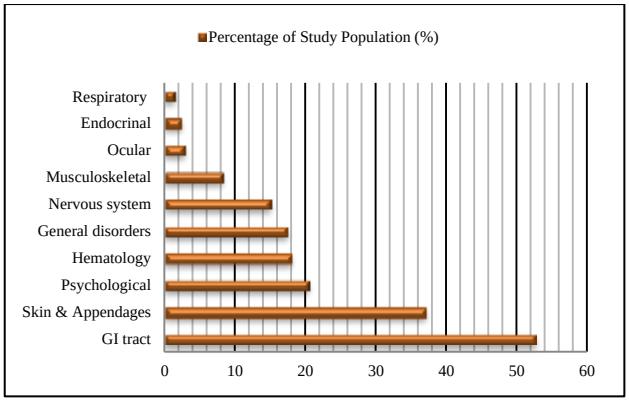


Figure 3: System wise profile of ADEs in the study population (N=205).

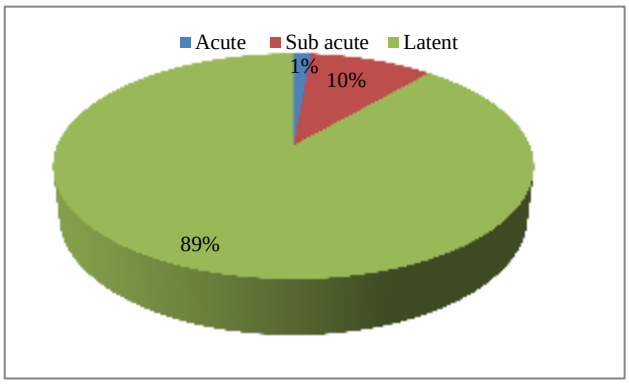


Figure 4: Onset of ADEs in the study population in percentages (n=635).

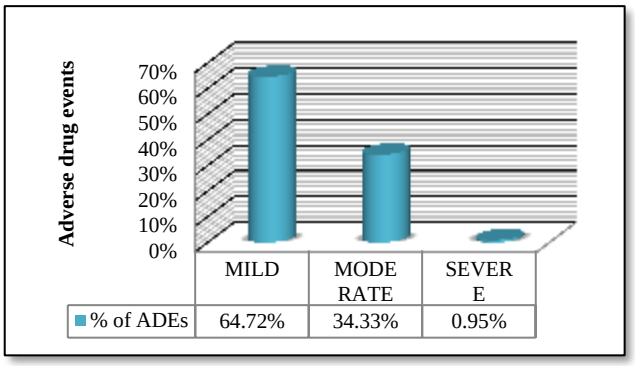


Figure 5: Severity of ADEs in the study population (n=635).

Table 2 shows the total number of adverse drug events (ADEs) recorded in the study population (N=205) was 635. Of them, 57 ADEs were found to be serious. Out of the 205 patients, 191 patients had at least one adverse drug event. This means that 93.17% of the study population experienced at least one adverse event. Amongst all the ADEs, highest percentage (38.53%) was documented for vomiting that occurred in 79 patients, followed by alopecia (35.61%), hyperpigmentation of skin and mucosa (29.75%) and anorexia (28.78%). Figure 3 shows the affected body systems with ADE. The most common system affected was GIT (52.68%). The onset of

adverse drug events in the study population was given in Figure 4.

Table 3: Treatment of ADEs in study population (N=205).

Event	Treatment	No. of ADE's
Leukopenia	Drug postponed/ G-CSF	26
Nausea and Vomiting	Increased dose of anti-emetics	37
Pain/ Fever	Analgesics/ Antipyretics	21
Anemia	PRBC transfusion/ Iron suppl.	16
Diarrhea	I.V. fluids/ ORS/ Anti-diarrheal	15
Stomatitis	Vitamin and Folic acid suppl.	11
Paraesthesia	Vitamin B12 supplements	11
Infections/ Induration	Antibiotics/ Local Treatment	10
Anorexia	Appetite stimulants	10
Alopecia	Hair regrowth agents (Minoxidil)	10
Constipation	Laxatives	9
Thrombocytopenia	Drug postponed	9
Heartburn	Gastric acid secretion inhibitor	6
Anastomotic leak	Re-anastomosis	3
Insomnia	Hypnotics	2
Mood changes	Anti-anxiety drugs	2
Weight loss	Protein supplements	2
Pruritis	Antihistamines	2
Convulsions	Anticonvulsants/ Electrolytes	2
Ascites	Ascitic tap	1
Diminished vision	Treatment stopped	1
Disorientation	Treatment stopped	1

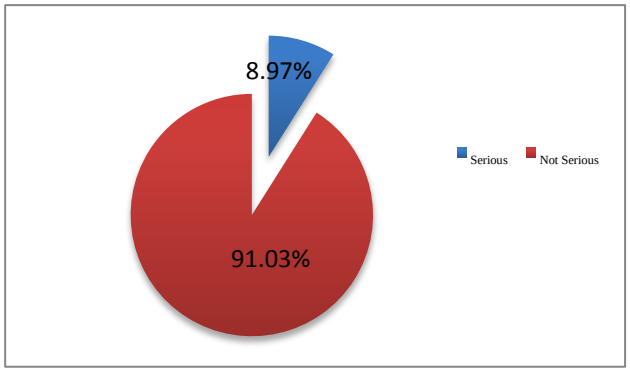


Figure 6: Seriousness of adverse drug events in the study population (n=635).

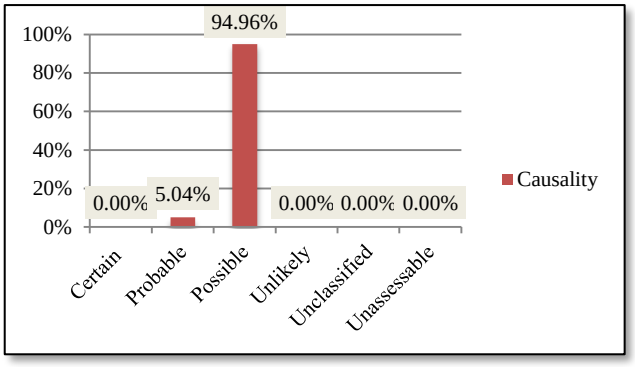


Figure 7: Causality of ADEs in the study population (n=635).

Figure 4 shows the onset of adverse drug events in the study population. 9 out of 635 adverse drug events (1.42%) had an acute onset, while 63 ADEs had a subacute onset (9.92%). The remaining 563 adverse drug events had a latent onset and comprised about 88.66% of the total ADEs. Figure 5 demonstrates the severity of adverse events including laboratory parameters. Out of 635, 411 were of mild severity, 218 moderate and 6 were severe. Figure 6 shows that out of the 635 adverse drug events, 57 ADEs were found to be serious. This means that 8.97% of the total recorded adverse events were of serious nature Causality assessment of the adverse drug events in the study population was presented in Figure 7. Majority of the events (94.96%) have been categorized under possible causality. The remaining 5.04% have been classified under probable category.

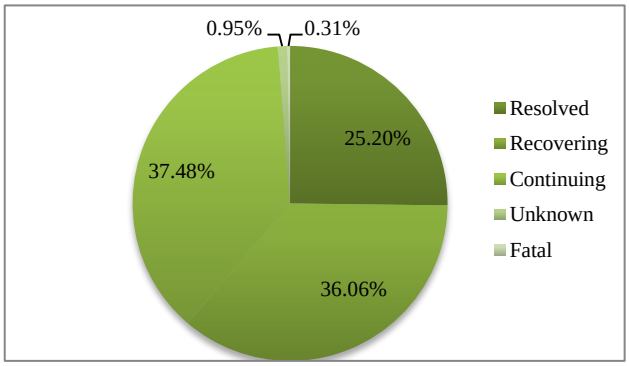


Figure 8: Outcome of ADEs in the study population (n=635).

Table 4: Gender-wise distribution of reactions in different age groups (n=635).

Age groups (Years)	Number of ADE in Males	Number of ADE in Females	Total No. of ADEs
18-30	20	44	64
31-45	73	111	184
46-60	107	164	271
> 60	48	68	116
Total	248	387	**635**

Table 5: Effect of gender as a risk factor for adverse drug events to occur in the study population (N=205).

Adverse events		Male	Female	Total	p value
Vomiting	Yes	47	32	79	0.008*
	No	51	75	126	
Mood swings	Yes	1	7	8	0.041*
	No	97	100	197	
	No	70	86	156	

*p value < 0.05 is significant.

Table 6: Effect of age as a risk factor for adverse drug events in the study population (N=205).

Event	Age group (in years)	Yes	No	Total	F value	Significance p value
Diarrhea	18-30	2	14	16	2.789	0.042*
	31-45	8	51	59		
	46-60	12	84	96		
	>60	10	24	34		

Table 7: Effect of prophylaxis on vomiting and nausea in the study population.

Emetic risk	No. of patients	Frequency (%)		Protection (%)	
		Vomiting	Nausea	Vomiting	Nausea
High	104 (51%)	45 (43%)*	29 (28%)*	59 (57%)	75 (72%)
Moderate	93 (45%)	34 (36%)*	28 (30%)*	59 (64%)	65 (70%)
Low	0	-	-	-	-
Minimal	8 (4%)	-	-	-	-
Total	**N=205**	**79**	**57**	**-**	**-**

Table 8: Adverse events of interest that occurred in the study population.

Event	Chemo-regimen	Frequency
Anastomotic leak	Oxaliplatin, 5-FU, Leucovorin	3
Hypomagnesaemia and Convulsions	Cisplatin, 5-FU	1
Blindness	Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone	1

Table 3 shows the treatment given for the adverse drug events in the study population. Figure 8 shows the outcome of adverse events in the study population after giving treatment to ADR's. Out of 635 ADE's, 160 events were resolved, 229 ADE's had a recovering outcome and 238 ADE's had a continuing outcome. 2 had a fatal outcome. They included a case anastomotic leak and a case of convulsions.

Table 7 explains the proportion of patients experiencing and not experiencing vomiting/ nausea in the presence of anti- emetic prophylaxis. Out of 205, 104 patients were prescribed highly emetic chemotherapy, 93 with moderately emetic chemotherapy while 8 patients with minimally emetic chemotherapy. After prophylactic therapy for nausea and vomiting, 59 patients (57%) received protection from vomiting while 75 patients (72%) received protection from nausea, in the highly emetic group, while 59 patients received protection from vomiting, 65 patients had protection from nausea in the moderately emetic chemotherapy. Table 8 presents the drug regimens that are responsible for causing significant adverse events like anastomotic leak, hypomagnesaemia and convulsions and blindness.

Table 8 represents adverse events of interest that occurred in the study population.

DISCUSSION

It is well known that antineoplastic drugs are the most commonly implicated class of drugs in causing adverse drug events in the patients which significantly diminishes the quality of life, increase hospitalizations, prolong

hospital stay and increase mortality.[1,14] It has been found that the ADRs profile of cancer chemotherapeutics is very sparsely reported and the situation is even worse in India.[15] The reason might be that the data collected by regulatory authorities and pharmaceutical industries is inaccessible to public. Hence, our study attempted to profile the documented adverse events with regards to their onset, seriousness, severity and causality to anti-cancer drugs. We also studied the effect of age and gender as risk factors for individual adverse events.

In our prospective pharmacovigilance study, we enrolled 213 patients of which 8 patients were withdrawn as they subsequently underwent radiotherapy. Amongst the 205 patients who were monitored serially for ADEs, found that breast cancer was the most common type of cancer affecting 27.80% of our study population. In a similar study, Poddar et al found that breast cancer had the highest prevalence (20%) amongst all other cancer types.[3]

The incidence of ADE's due to anticancer drugs in our study was about 93% (191 patients). This finding is similar to the study by De, which gave a 98.79% incidence of ADEs in cancer patients hospitalized for receiving anticancer chemotherapy.[16] The high incidence is because chemotherapeutic drugs have a narrow therapeutic index and the dosage needed to achieve a therapeutic response usually proves toxic to body's rapidly proliferating cells.[3]

In our study, the GIT was the most commonly affected system i.e. around 52% of the study population. In contrast it was found that hematological system was most commonly affected in about 40% of the study population, followed by GIT at 33% in a study conducted by Mallik et al in Nepal.[17]

The most commonly observed ADE's in the present study was vomiting affecting 38.53% of the study population that were comparable to the study of Poddar et al, that was documented in 52% of the study population.[3] In a study by Lau et al to evaluate the ten most common adverse drug reactions in oncology patients, nausea with/without vomiting was found to be the second most common adverse event after constipation.[18] Constipation less commonly occurred in about 7% of our study population.

The onset of ADE's was latent in 88.66% cases in our study. In a study by Mallik et al, the onset of the ADEs was found to occur within a day in 44% of their population.[17]

In the present study, out of the recorded 635 events, 57 were found to be serious. Thus, 8.97% of the total ADEs in our study were of serious nature. In a similar study by De, the author found that the incidence of serious ADEs was 5.76%.[16] As per the modified Hartwig Siegel scale, the percentage of severe ADE's in our study was as low as 0.95 %. While in the study by De, the severe ADEs were comparatively higher at 9.83%.[16] Causality assessment of our study classified majority of the adverse events under 'possible' category (94.96%), as most of the patients were on more than one anti-cancer drugs. The remaining events (5.04%) came under the 'probable' category. In a study by De, the documented causality was certain in 1.84% events, probable in 85.28% events and possible in 12.88% events.[16]

Rademaker mentions that the treatment related toxicity is more common in females; generally 1.5 to 1.7 folds than men.[19] This was consistent with the findings of our study. Similar observations were also noted by Poddar et al and Blacker et al. The reason for sex-selective toxicity could be attributed to the various stages female gender undergoes, like pregnancy, menarche etc. during which, there is an alteration in the pharmacokinetics and pharmacodynamics properties of the drugs.[3,20]

The frequency of mood swings was significantly common in females in our study. Out of the 7 women who suffered from mood swings, 4 women were on concomitant hormone therapy for breast cancer. This might be the probable reason behind mood swings being more common in females.

The frequency of adverse drug events in our study was more in the age group of 46-60 years as compared to the other age groups. This was in accordance to the findings of Poddar et al where maximum number of adverse events was in the age group of 41-50 years.[3]

In this study age factor was also considered as a risk factor for the incidence of ADE's. The incidence of diarrhea in the age group of >60 years was significantly higher than 18-30 years of age. This findings commensurate with the observation of Guo et al where maximum proportion (42%) events occurred in age group >60 years, suggesting that incidence of adverse reactions increases with age.[21] The reason could be that in elderly patients, the metabolizing capacity and the excretory functions are generally diminished leading to accumulation of drugs in the body and thus increasing the risk of ADRs.[22]

In our study, it was observed that use of anti-emetic prophylaxis prevented vomiting in about 57% and nausea in about 72% patients receiving highly emetic chemotherapy, respectively. In patients receiving moderately emetic chemotherapy, anti-emetic prophylaxis prevented vomiting in about 64% and nausea in about 70% patients, respectively. Wickham in her article mentions that, even with prophylaxis with best anti-emetic regimens, 20-30% patients will experience delayed nausea and vomiting.[23] From these figures, we may conclude that the delayed vomiting was not sufficiently controlled in our study population.

A few of the patients in our study experienced some significant life threatening adverse events like

anastomotic leak, convulsions and blindness. The three cases of anastomotic leak were seen in patients receiving 5- Fluorouracil (5-FU) and Oxaliplatin. Findings of the study by Ersoy et al indicated that Oxaliplatin is less detrimental to the healing of colonic anastomoses, when administered on days 1 and 5 after resection, than 5-FU.[24] Ozel et al, Kanellos et al, Morris in their experimental study, concluded that intravenous 5-FU delayed, but did not prevent healing, and that it would be safe to use it in the postoperative period, but not until several days after operation.[25-27] In this study seizures was noted in 1 case. This might be due to hypocalcemia and hypomagnesemia in patients that receive intensive chemotherapy, especially cisplatin, with over- hydration. This can be easily prevented by magnesium and, calcium supplementation during the chemotherapy infusion.[28] In our study immune-compromised female patient suffering from non-Hodgkin's lymphoma after 2 months of chemotherapy developed bilateral optic neuritis. However, as either the drug (vincristine) or the disease (HIV) or both could have been the causative factor for blindness, we implicated that; vincristine is the possible causative agent for this catastrophic phenomenon.

The limitations of the study were the patients were required to be motivated to report adverse events that occurred between two cycles otherwise it was not possible to ascertain causality for any particular drug as regimen comprised of more than one drug. Re-challenge or de-challenge could not be performed in many events. Since, this study is limited to less number of populations, less time period, limiting to a particular type of cancer, or a group of anti-cancer drugs, similar pharmacovigilance studies with longer duration of time covering larger sample size, by including all types of cancer and their treatment regimens are needed, to make the causality assessment more predictable.

CONCLUSION

Anticancer agents have a very high risk of ADRs that should be monitored. Pharmacovigilance offers a great deal in minimizing the ADRs by modifying the dose of the drugs and by reducing the financial burden to the patient and to the society. There is a great need in setting up an effective ADR monitoring system in order to enhance the quality of the life of the patient.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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