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Original Article

Oncology Section

Drug Utilisation Pattern and Adverse Drug Reactions in Stage II Breast Cancer Patients in a Tertiary Care Centre of Odisha- An Observational Study

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ABSTRACT

Introduction: Breast cancer is the most common cancer occurring in women with an estimated prevalence of 28.94% in Cuttack, Odisha, India. Adverse Drug Reactions (ADRs) associated with the use of anticancer drugs is a worldwide problem which needs further attention.

Aim: To know about treatment regimens, premedications used for toxicity amelioration or any associated ADRs occurring during treatment of stage II breast cancer patients.

Materials and Methods: This was a prospective observational study carried out in the Department of Pharmacology in collaboration with Acharya Harihar Regional Cancer Center (AHRCC), SCB Medical College and Hospital, Odisha, India. A total of 181 female breast cancer patients of stage II were finally analysed about their treatment protocol pattern including premedication, chemotherapy regimen, associated ADRs and their treatment. Different outcomes measured were Absolute Neutrophil Count (ANC), febrile neutropenia, anaemia, thrombocytopenia. ADRs were analysed by using World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) Scale and Hartwig-Siegel Scale. All analysis was performed using Statistical Package For the Social Sciences (SPSS) version 18.0.

Results: Most common chemotherapy combination regimen used was cyclophosphamide+doxorubicin+paclitaxel+trastuzumab in 30.9% of patients, out of which 28.7% showed ADRs. Ondansetron and aprepitant were commonly used as premedication in 96% of patients. Most commonly reported ADR was Chemotherapy Induced Nausea and Vomiting (CINV) in 43.6% patients and Chemotherapy Induced Neutropenia (CIN) (34.8%). Fifty percent ADRs were mild and 3.3% ADRs were severe in nature. A 64% ADRs were possible and 23% ADRs were probable according to WHO-UMC causality assessment scale. Grade 4 Neutropenia was present in 1.3% patients. Mild haematological problems were treated by blood transfusion while severe cases by additional growth factor support like Granulocyte Colony Stimulating Factor (G-CSF). In this study, mean age of presentation was found to be 44.6 years.

Conclusion: Despite use of drugs for toxicity amelioration, some grade four life threatening ADRs were observed. Mostly ADRs were missed and under-reported. Regular monitoring, increased care and patient compliance was needed to detect new ADRs and to reduce the morbidity as well as burden on the patients.

Keywords: Causality assessment, Chemotherapy, Neutropenia

INTRODUCTION

Drug utilisation research has an important role in clinical practice now-a-days at both state and national level. It is the basis for formulating the strategies and policies in different hospitals or healthcare centres. The main aim of such research is facilitating rational use of drugs, utilising health resources in the best possible way, which is mostly important in a developing country like India where 72% of healthcare burden is on the patients [1].

As per Indian Council of Medical Research (ICMR), among the various cancers occurring in women, breast cancer is the most common with an estimated 1.67 million new cancer cases in 2012 [2]. The estimated incidence of cancer cases in Cuttack, Odisha in 2014 was 38,375 and estimated mortality due to cancer was 16,885; amongst these, breast cancer being the leading cause of cancer in females (28.94%) [3].

The treatment of cancer aims at providing cure; if cure is not possible then palliation i.e., best possible treatment to prolong the life as much as possible [4]. Chemotherapy is a part of multimodal approach for treatment of many tumours [5]. It is the first approach for treatment of stage 1 and stage 2 breast cancer patients while for stage 3 and 4, mostly radiation or surgery is done [6,7]. Cell Cycle Non Specific (CCNS) drugs acts on dividing as well as resting phase of cells CCNS used in breast cancer are cyclophosphamide, doxorubicin, daunorubicin, cisplatin etc., Cell Cycle Specific (CCS) drugs acts on proliferating cells such as paclitaxel, epirubicin, 5 flurouracil etc., [8].

Chemotherapy drugs have a narrow therapeutic index. They target cancer cells and the fast-growing normal cells of skin, hair, intestine and bone marrow as well. Frequent use of chemotherapy causes CINV, alopecia, and CIN. CIN is the most common haematological toxicity [3,8]. It is especially seen with the advent of the more efficacious chemotherapeutic regimens and individual patient risk factors, example no-taxane containing regimens for breast cancer [9-12].

As per World Health Organisation (WHO), ADR is defined as any response to a drug which is harmful and occurring at normal doses when used for prophylaxis, identification or treatment of disease, or for alteration of biological function in humans [13]. ADR due to chemotherapy can be mild to severe and can be life threatening, so it needs further attention. Mild haematological problems due to chemotherapy are treated by blood transfusion and/or component therapy. Moderate to severe cases need additional G-CSF [14]. Neutropenia associated with fever are oncological emergency and need in-patient hospitalisation and further antibiotic coverage as per Infectious Diseases Society of America (IDSA) guidelines [15]. The risk of infection increases and become fatal with decreasing Absolute Neutrophil Count (ANC) i.e., in Grade 3 and grade 4

neutropenia (ANC <1000 and 500/μL, respectively) [16,17]. Such infections even when managed with only broad spectrum antibiotics can lead up to 10% in-patient mortality [16].

A very little information is available regarding patterns of care followed in breast cancer patients [5,9,10]. Therefore, this study focused on different treatment patterns (different chemotherapy combinations used), premedication followed for toxicity amelioration, any associated ADRs during treatment protocol and their management.

MATERIALS AND METHODS

This was a hospital based, prospective observational study conducted at Department of Pharmacology of Sriram Chandra Bhanja Medical College and Hospital (SCBMCH), in collaboration with Department of Medical Oncology in the female ward of AHRCC, Cuttack, Odisha among breast cancer patients from November 2015 to October 2017. AHRCC is one of the 25 recognised cancer centres in India. It provides comprehensive palliative care which makes it a reliable cancer center in this zone.

Before starting the study, prior approval was obtained both from the Institutional Ethics Committee (IEC) SCBMCH and Ethics Committee of AHRCC (060-IEC-AHRCC). Written informed consent was taken from patients before including into study according to eligibility criteria.

Inclusion criteria: Female breast cancer patients of age group 18-80 years confirmed by histopathology examination done in Department of Oncopathology AHRCC or SCB Medical College Pathology laboratry were enrolled in the study. The patients were classified according to AJCC manual, 6th edition into Stage II a and II b [6].

Exclusion criteria: This study excluded pregnant women, patients who were on concomitant radiotherapy within 4 weeks of enrolment, with any other malignancies, history of bone marrow or stem cell transplantation.

Sample size calculation: Taking into account the prevalence of breast cancer among women (14%) [3], sample size has been calculated by formula which comes to 185:

$n=Z^2_{1-\alpha/2}\times P(1-P)/D^2$

Study Procedure

A total of 200 breast cancer patients were included in the study, out of which 19 were lost to follow-up and 181 patients were included in final analysis.

Data of selected and screened patients were collected in a pre-designed Case Record Form (CRF) by study group. Demographic variables including age, weight, Body Surface Area (BSA) and the treatment protocol of the patients, including pre medications, chemotherapy regimen, and cycle duration were noted. Routine laboratory investigations, i.e., Complete Blood Count (CBC) were done and other bedside parameters like Blood Pressure (BP), pulse, pallor, icterus, body temperature etc., were recorded on a daily basis during stay. Data was taken before and after every cycle of chemotherapy. Follow-up was done and patients were examined in each cycle.

Different Parameters Studied

At the end of study, ANC in each cycle, incidence of febrile neutropenia, anaemia (grade 2 and 3) and thrombocytopenia was measured. ADRs occurring during chemotherapy was also observed. ADRs were classified according to their severity by using Hartwig-Siegel Severity Assessment Scale and Causality assessment for each ADR was done by WHO-UMC causality assessment system [18,19]. Rechallenge test was done in some of the cases to assess some ADRs which were certain. Requirement of blood transfusion and/or fresh frozen plasma needed for ADR management was analysed.

The National Comprehensive Cancer Network (NCCN) guidelines were followed for all the chemotherapy regimens [7]. These combination regimens were categorised in three different groups according to number of anticancer drugs in each regimen. The patient receiving two cytotoxic drugs were placed in category one, category two included patients who were on three cytotoxic drugs and Category three included patients who were on combination of two cytotoxic drugs with monoclonal antibody. Rate of neutropenia, ANC count and other haematological ADRs were assessed as per Common Terminology Criteria for Adverse Events (CTCAE V 3.0) guidelines [20].

STATISTICAL ANALYSIS

All the data were entered in specially designed CRF. Information was entered and analysis done by using Microsoft Excel 2010 spreadsheet. All analysis was performed using SPSS version 18.0. Categorical variables were represented as frequency and proportion. Chi-Square test was done to analyse the association of ADRs between different chemotherapy categories regimen.

RESULTS

The total number of patients screened for the study was 200 but out of them 181 patients were found eligible for final analysis. The age distribution among patients is given in [Table/Fig-1]. Most of the patients 76 (42%) were having BSA distribution less than 1.5 m^2 according to which the dosage of chemotherapy regimen were calculated and given to patients.

Age group (years)	N (%)
25-34	28 (15.5)
35-44	59 (32.6)
45-54	55 (30.4)
56-75	39 (21.5)

[Table/Fig-1]: Age distribution among patients

Out of 181 patients, 165 (91%) patients have experienced at least one ADR during their treatment course. Most common regimen used in this study was doxorubicin+cyclophosphamide+ paclitaxel+ transtuzumab in 56 patients (30.9%), in which ADR was reported in 52 (28.7%) patients. Maximum number of ADRs (238 out of 843) was due to this regimen. Cyclophosphamide (C) was used in all above regimens [Table/Fig-2]. Hormonal agents like tamoxifen, anastrozole were prescribed to four patients. The patients receiving two cytotoxic drugs were placed in category one (33 patients). Category two included patients who were on three cytotoxic drugs and category three included patients who were on combination of two cytotoxic drugs with monoclonal antibody (72 patients each). Among the ADRs involving gastrointestinal tract, CINV was more significant in category three patients affecting 79 (43.6%) of patients. Diarrhoea and bleeding episodes were more common in category three patients and it was statistically significant, while more episodes of neutropenia occurred in category two patients [Table/Fig-3,4].

In this study, chemotherapy induced grade 2 and grade 3 anaemia was found in 132 cycles of patients. There were 72 episodes of

Chemotherapy used	Total number of patients, n (%)	ADR, n (%)	Total ADRs
AC+T+Tt	56 (30.9)	52 (31.5)	238
TAC	37 (20.4)	33 (20)	174
AC+T	31 (17.1)	26 (15.7)	114
AC	23 (12.7)	22 (13.3)	110
EC+T+Tt	16 (8.8)	14 (8.4)	112
EC	10 (5.5)	10 (6.1)	52
FEC	8 (4.4)	8 (4.8)	47
Total	181	165	847

[Table/Fig-2]: Treatments patterns observed in the study.
A: Doxorubicin; C: Cyclophosphamide; T: Paclitaxel; Tt: Transtuzumab; E: Epirubicin; F: 5-Fluorouracil

ADRs	Patients (n)	Percentage (%)
Nausea and vomitting	79	43.6
Gastritis	70	38.6
Pain	71	39.2
Alopecia	68	37.6
Neutropenia (CIN)	63	34.8
Infection	61	33.7
Anaemia	61	33.7
Myalgia	45	24.9
Oral ulcers (OU)	43	23.8
Fever	36	19.9
Loss of appetite	35	19.3
Sleep changes/Insomnia	30	16.6
Constipation	29	16
Thrombocytopenia (TH)	26	14.4
Diarrhoea	23	12.7
Allergy	15	8.3
Neuropathy	12	6.6
CVS dysfunction (CVS D)	10	5.5
Hepatomegaly	10	5.5
Headache	9	5
Anxiety	7	3.9
Cough	6	3.3
Acute kidney injury	5	2.8
Bleeding	4	2.2
Others*	29	12.7
Total	847	

[Table/Fig-3]: Adverse Drug Reactions (ADR) observed in this study (N=181).
*rash 4 (2.2%), breathlessness 4 (2.2%), granulocytosis 2 (1.1%), hiccups 2 (1.1%), hypotension 2 (1.1%), cholelithiasis 3 (1.6%), colic pain 3 (1.6%), lymphocytosis 3 (1.6%)

Sl. No.	ADRs	Category one (n=33)	Category two (n=72)	Category three (n=72)	Total (n=181)	p-value (Chi-square test)
1	Haematological					
	CIN	5 (13.5)	39 (54.1)	19 (26.3)	63 (34.8)	0.04
	Anaemia	14 (37.8)	24 (33.3)	23 (31.9)	61 (33.7)	0.824
	Thrombocytopenia	4 (10.8)	3 (4.2)	1 (1.4)	8 (4.4)	0.076
2	CINV	12 (32.4)	33 (45.8)	34 (47.2)	79 (43.6)	0.300
3	Gastritis	13 (35.1)	30 (41.7)	30 (41.7)	73 (40.7)	0.07
4	Pain	21 (56.8)	25 (34.7)	25 (34.7)	71 (39.2)	0.05
5	Alopecia	13 (35.1)	22 (30.6)	33 (45.8)	68 (37.6)	0.157
6	Infection	15 (40.5)	23 (31.9)	23 (31.9)	61 (33.7)	0.615
7	Myalgia	11 (29.7)	15 (20.8)	19 (26.3)	45 (24.9)	0.553
8	Oral ulcers	8 (21.6)	20 (27.8)	15 (20.8)	43 (23.8)	0.584
9	Neuropathy	7 (18.9)	2 (2.8)	3 (4.2)	12 (6.6)	0.003
9	Diarrhoea	4 (10.8)	4 (5.6)	15 (20.8)	23 (12.7)	0.02
10	Constipation	8 (21.6)	13 (18.1)	8 (11.1)	29 (16)	0.305
10	Decrease appetite	8 (21.6)	15 (20.8)	12 (16.7)	35 (19.3)	0.757
11	Bleeding	0	0	4 (5.6)	4 (5.6)	0.045

[Table/Fig-4]: Pattern of Adverse Drug Reactions (ADR) in different chemotherapy combinations.
CIN: Chemotherapy induced neutropenia

neutropenia, out of which 44 were of grade 3, 18 were of grade 2 and 10 episodes were of grade 4 neutropenia [Table/Fig-5].

Common premedications used were Ondansetron (96.6%) and Dexamethasone (88.4%) [Table/Fig-6]. G-CSF (Filgrastim/Pegfilgrastim) were administered in total of 500 cycles for neutropenia. Blood transfusion were given to 50 patients for severe anaemia. According to WHO-UMC Category, 64% ADRs were possible and 23% ADRs were probable according to WHO-UMC Causality Assessment Scale

ADRs	Total cycles
Neutropenia	
Grade 2	18
Grade 3	44
Grade 4	10
Leukopenia	
Grade 2	25
Grade 3	9
Anaemia	
Grade 2	123
Grade 3	9
Thrombocytopenia	26

[Table/Fig-5]: Types and severity of haematological Adverse Drug Reactions (ADR).

Premedicatios	Number of patients (n=181)	Percentage (%)
Ondansetron/Domperidone	175	96.6
Dexamethasone	160	88.4
Ranitidine	139	76.8
Aprepitant	54	29.8
Pheniramine maleate and Hydrocortisone	52	28.7
Promethazine	10	5.5

[Table/Fig-6]: Premedications used in patients.

[Table/Fig-7]. 50.1 percent ADRs were mild and 3.3% ADRs were severe in nature according to Hartwig-Siegel Scale [Table/Fig-8].

WHO-UMC category	Frequency (n)	Percentage (%)
Certain	84	9.4
Probable	196	23.2
Possible	543	64.4
Unlikely	24	2.833
Total	847	100

[Table/Fig-7]: WHO-UMC causality assessment of ADRs.
Rechallenge Test was positive in 84(9.9%) patients

Hartwig-siegel scale	Frequency (n)	Percentage (%)
Mild	424	50.1
Moderate	395	46.6
Severe	28	3.3
Total	847	100

[Table/Fig-8]: Classification of ADRS.

DISCUSSION

Cancer related ADRs are very common and affecting quality of life. According to literatures the highest incidence of ADRs were seen among regimen used in breast cancer patients [6,7,12,21,22]. A study by Chopra D et al., has shown the incidence of ADRs as 39.1% [23]. Despite regular use of premedications, the occurrences of ADRs are increasing.

The AHRCC plays a key role in cancer registry through its wide laboratory network across the country which helps to assess the cancer burden in the country [24]. A total of 200 patients were screened during the course of study and in the end a total of 181 patients were included in final analysis. The mean age of presentation was 44.6 years which is less compared to other studies [25,26]. Most common chemotherapy regimen used was Cyclophosphamide+Doxorubicin+Paclitaxel+Trastuzumab. Ondansetron and dexamithasone were commonly used as premedication in many patients. Most common reported ADR was CINV, gastritis, pain,CIN etc.. Haematological system was most commonly affected. Out of all ADRs, 50% ADRs were mild. Sixty four percent ADRs were possible according to WHO-UMC Casuality Assessment

Scale. There were some cases of severe Grade 4 ADRs also. ADRs were treated with different medications according to severity.

In this study, ADRs mostly occurred in the age group of 41-50 years and this finding is similar to studies by Poddar S et al., and Kirthi C et al., [14,27]. Most of the patients (42%) were having BSA distribution less than 1.5 m^2 according to which the dosage of chemotherapy regimen was calculated.

Majority of patients 147 (88.3%) were started with cytotoxic drug combination of Doxorubicin and Cyclophosphamide (AC) and in later stages taxanes were added to cytotoxic combination regimen. The addition of taxanes improved the efficacy of chemotherapy, but at the cost of increased non cardiac toxicity [17,28,29]. In this study 174 (96%) of the patients were treated with alkylating agents out of which 140 (77%) patients were on taxane-based regimen with AC. In contrast to this finding, Kumar S et al., reported that out of 500 patients, 295 (59%) received anthracycline regimen and 123 (24%) received taxane-based regimens with AC [26].

Out of 181 patients, 165 (91%) patients have experienced at least one ADR during their treatment course and this finding resembles a study by Medhi B et al., [30]. As compared to studies by Poddar S et al., and Jose J and Rao P, this study also found that most commonly used class of drugs were antimetabolites and alkylating agents, which were responsible for causing ADRs [14,15]. In a study, when analysed, alkylating agents have shown ADR in 52% patients followed by antimetabolites in 20% patients [9]. Trastuzumab was given to 72(39.7%) patients in this study while in other studies it was given to only 4.6% and 2% patients respectively [26,30]. Surprisingly, the results of this study resemble Medhi. B et al., who have shown that 5-FU, epirubicin, cyclophosphamide (FEC) was prescribed to 8 (4.4%) of patients and all have developed ADRs [30].

As many studies have focused on ADRs caused due to chemotherapy drugs, but there were very few studies which focus on pattern of ADRs in chemotherapy combination regimen [31-33]. In this study, patients receiving chemotherapy regimen were categorised in three different groups. The patients receiving two cytotoxic drugs were placed in category one (33 patients). Category two includes patients who were on 3 cytotoxic drugs and Category three included patients who were on combination of two cytotoxic drugs with monoclonal antibody (72 patients each).

This study shows that ADRs affected haematological system most frequently followed by gastrointestinal tract and this finding is supported by Mallik S et al., and Sharma A et al., [9,31]. All the haematological ADRs 150 (72%) patients in this study were classified according to CTCAEV grading system [20]. Chemotherapy kills cancer cells as well as rapid dividing normal cells of bone marrow resulting in myelosuppression thus affecting WBCs, platelets and RBCs. Among the haematological ADRs, neutropenia resulting from chemotherapy (CIN) may be life threatening. In this study CIN was more common in catagory 2 patients compared to other two groups (p-value 0.04).

Among the ADRs involving gastrointestinal tract, CINV was more significant in catagory 3 patients affecting 79 (43.3%) of patients. Chopra D et al., and Kaur K et al., in their studies have shown CINV affecting 25% and 39% of patients respectively [23,33]. Patients who received AC+T therapy (catagory 2) suffered from gastritis 70 (38%) and pain 71(39%) which is more than the catagory 1 patients. While in other study patients on AC+T Regimen complained of peripheral neuropathy, arthralgia and leucopenia [25]. Neuropathy in this study was more common in patients having paclitaxel (two drugs) regimen and it was statistically significant (p-value 0.003).

Diarrhoea and bleeding episodes were more common in category three patients and it was statistically significant, while more episodes of neutropenia occurred in category two patients. In other study, 7% patients have suffered from diarrhoea [24]. Alopecia was documented in 68 (37.6%) of patients in this study which was due to cytotoxic and transtuzumab therapy compared to 21% as shown by Chopra D et al., [23]. Oral ulcers/stomatitis 43 (23.8%) were more in category two patients and this finding resembles Kaur K et al., [33]. There should be a special mention about some ADRs due to particular drugs. Two incidence of severe hiccups due to cyclophosphamide occurred and were managed in hospital. Two cases each of granulocytosis episodes and hypotension episodes and three cases of lymphocytosis were reported in patients receiving regimen (AC+T) and (AC+T+Tt), respectively. Four patients suffered from severe rash due to taxanes. Three patients suffered from cholelithiasis, four from breathlessness and three from colic pain during the treatment cycle.

According to literature, febrile neutropenia or Grade 3/4 neutropenia is relatively common among the haematological ADRs in breast cancer patients [23]. Chemotherapy regimens have also found to induce or aggravate anaemia [23]. Upto 23% of the breast cancer patients experience at least one episode of febrile neutropenia during standard chemotherapy and this figure is increased up to 98% in patients exposed to high-dose chemotherapy regimens [23]. Measures were taken to overcome severe anaemia and neutropenia in these patients according to severity and chemotherapy combination profile. In this study, there were 72 episodes of neutropenia, out of which 44 were of grade 3, 18 were of grade 2 and 10 episodes were of grade 4 neutropenia as compared to Mallik S et al., who found grade 1 neutropenia as the commonest type (28.6% patients) [9]. G-CSF is used both for prevention and treatment of neutropenia according to NCCN guidelines [7]. Filgrastim/Pegfilgrastim were administrated in total of 500 cycles to the patients in this study. Chemotherapy induced grade 2/3 anaemia were found in 132 cycles of patients. A total of 50 (27.6%) patients were administered blood transfusion for severe anaemia. This finding is surprisingly higher in contrast to patients receiving blood transfusions (9.3%) as shown by Othieno-Abinya N et al., [34].

Different scales are available for assessing ADRs i.e., WHO-UMC system, Naranjo's Scale (for causality assessment), Hartwig and Siegel Scale (for severity assessment) and Modified Schumock and Thornton criteria (for preventability assessment) [18,19,31,35]. This study shows 27 cases of severe ADRs while Chopra D et al., and Anjum F et al., have shown 764 severe cases and 1 severe case respectively [23,25]. There were 422 (50.1%) cases of mild ADRs and 394 (46.6%) cases of moderate ADRs as reported in this study. One study by Chopra D et al., was reported with 514 (86.97%) mild ADRs and 76 (12.8%) moderate ADRs [23]. In this study four cases and two cases each of grade 3 and grade 4 vomiting were found, respectively. Seven cases of grade 4 diarrhoea, six cases of grade 4 constipation were also found. Causality assessment of ADRs was done using WHO-UMC assessment scale. 543 (64%) ADRs were possible, 196 (23%) were probable and 80 (9%) were certain in this study as compared to other studies where 35% and 31% of ADRs were possible, 64% and 62% of ADRs were probable and 6% ADRs were certain [30,36]. Re-challenge test was positive in some cases which makes those ADRs as certain.

The ADRs were managed with different medications. Half of the ADRs required treatment. Injection ondansetron was the most common drug used for managing the ADRs followed by filgrastrim, blood transfusion, dexamethasone, and ranitidine in this study as well as in a documented study [21]. It was observed that majority of patients had received antiemetic as preventive therapy including dexamethasone (88.4%). This is consistent with findings of some other studies where majority of the cases received increased doses of antiemetic in order to manage ADR [9,14]. Nevertheless with the use of premedication, it has failed to prevent ADRs completely. This indicates that current ADR prevention and management practices require attention. Enhanced use of preventive measures and early detection of drug toxicity has the potential to contribute to reduce the severity of ADRs.

Limitation(s)

This study has not focused upon the preventability of ADRs.

CONCLUSION(S)

The analysis of different treatment patterns showed that most common regimen used in the treatment of breast cancer was combination of cyclophosphamide, doxorubicin, paclitaxel and transtuzumab. The three drug regimen caused more ADRs as compared to two drug regimen. The most common ADR was CINV, but the most commonly affected system was haematological system. Despite use of drugs for toxicity amelioration, some grade 4 life threatening ADRs were observed. Many times ADRs are missed and under-reported which have affected the quality of life of patients. Regular monitoring, increase care and patient compliance is needed to reduce the morbidity and burden for patients.

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