University Journal of Pre and Para Clinical Sciences

ISSN 2455–2879 2020, Vol.6(8)

PATTERN OF ADVERSE DRUG REACTIONS OF ANTICANCER DRUGS USED IN PATIENTS WITH BREAST CANCER IN A TERTIARY CARE HOSPITAL

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Abstract : Adverse drug reactions (ADRs) are one the leading causes of morbidity, so monitoring adverse drug reactions are helpful in improving patientsquality of life. Anti-cancer drugs are prone to cause ADRs and there is lack of pharmacovigilance data on such drugs. The aim of our study is to monitor the pattern of adverse drug reactions of anticancer drugs in patients with breast cancer in a tertiary care hospital. The study was conducted in Department of Oncology of Govt. Stanley Medical College, Chennai as an open observational study . Adverse drug reactions are monitored and documented using a questionnaire based adverse drug reaction reporting form drafted from CDSCO. Out of the total 60 patients, 54 patients (90) reported of having adverse drug reactions. Nauseavomiting was the more predominant adverse drug reactions. Causality assessment using Naranjos algorithm, 96.3 of adverse reactions were classified as possible and 3.7 were classified under probable adverse reactions. The adverse event prevalence suggests that practically all patients receiving cytotoxic drugs suffer one or more ADRs. So, early detection of drug toxicity may help in modifying the doses and premedication can be given to minimize the toxic effects. Similar studies if conducted in other centres will be able to tell us the percentage of such adverse drug reactions and incidence of other adverse drug reactions which were not occurred in this study.

Keyword : Adverse drug reactions, Anticancer drugs, Pharmacovigilance, Naranjos algorithm.

INTRODUCTION:

An Adverse drug reaction (ADR) is defined by WHO as “A response to a drug which is noxious & unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function” (1) Adverse drug reactions are a global problem which burdens the society. Sometimes the ADRs are so serious & severe that, the cost needed to control the morbidity & mortality is more than the cost to treat the actual disease. Breast cancer is a malignant proliferation of epithelial cells lining the ducts or lobules of the breast. It is the most commonly occurring cancer in females worldwide, with an age-standardized incidence rate of 39.0 per 100,000 women. In India, age-standardized incidence rate is about 22.9 per 100,000 women.(2) The female: male ratio is 150:1.(2)The risk factors are positive family history, early menarche, late menopause, nulliparous women, lack of lactation, perimenopausal women, proliferative breast disease, oral contraceptive pills intake, H/O hormone replacement therapy, genetic predisposition, obesity& irradiation. Breast cancer responds to multiple chemotherapeutic agents, including anthracyclines, alkylating agents, taxanes and antimetabolites. Multiple combinations of these agents have been found to be more helpful in breast cancer patients in stages IIa, IIb, IIIa, IIIb, IIIc, IV in the form of adjuvant or neoadjuvant or palliative chemotherapy. These drugs themselves can cause adverse drug reactions which shall affect the patients’ health. Many of the adverse effects of anticancer drugs are an extension of their therapeutic action, which is not selective for malignant cells but affects all rapidly dividing cells(3). Anticancer drugs very often show ADRs. Nausea,vomiting, myelosuppression, mucositis etc. are very common ADRs due to cancer chemotherapy (4) .When the ADRs due to anticancer drugs are compared to the development of total ADRs, then also nausea/vomiting shows a very high % as revealed in one study from South India (5)

AIM & OBJECTIVE:

To study the pattern of ADR of anticancer drugs in patients with breast cancer in a tertiary care hospital.

MATERIALS & METHODS:

Study Centre: Department of Oncology, Govt. Stanley Hospital, Chennai-1

Study Design: Retrospective, observational study.

Study Duration: April 2013- September 2013

Study Population: Breast cancer patients in Oncology department.

Sample size: 60 patients with breast cancer receiving chemotherapy.

Inclusion Criteria:

(1) Age 25-70 years
(2) Both males & females.
(3) Patients under TNM stages IIa, IIb, IIIa, IIIb, IIIc& IV (6).
(4) Patients receiving multiple combinations of anticancer drugs as adjuvant or neoadjuvant or palliative chemotherapy.

Exclusion Criteria:

(1) Age <25 &>70 years.
(2) Patients with TNM stages 0&1.(6)
(3) Patients receiving drugs for other cancers.
(4) Patients with past H/O gastrointestinal or hematological disorders.

(5) Patients with past H/O renal disease or liver disease.
(6) Patients with past H/O CVS or CNS diseases.

STUDY PROCEDURE

This study was conducted in Department of Oncology, Govt. Stanley Hospital after obtaining approval from the Institutional Ethical Committee. This was a hospital based, retrospective, observational study from April 2013 to September 2013 among 60 breast cancer patients receiving anticancer drugs. The following parameters were recorded.

v Age
v Gender
v Diagnosis
v Anti cancer drugs prescribed
v Adverse drug reaction pattern
- Incidence
- Severity

Based on the age, sex, chemotherapy and symptoms given by the patients' statistical analysis was done & results were obtained. ADRs documented in suspected ADR reporting forms designed by CDSCO and causality assessment was done using Naranjo's scale and severity by modified Hartwig Siegel scale.

RESULTS:

The datas were entered into Excel spread sheets and descriptive statistics was used to analyze the data at the end of the study. Out of 60 patients observed for ADR, 54 patients had ADR. The following anticancer drugs were used for breast cancer in Dept of Oncology, Govt. Stanley Hospital.

v **Group I** à Inj.Doxorubicin 60mg/m2 BSA slow IV every 3 weeks, +Inj.5FU 500mg/m2 IV infusion weekly for 6-8 week, +Inj.Cyclophosphamide 15 mg/kg IV every 7-10 days.
v **Group II** à Inj.Gemcitabine 1 g/m2 IV weekly for 7 weeks, +Inj.Etoposide 50mg/m2/day IV for 5 days.
v **GroupIII à** Inj.Paclitaxel 150mg/m2 IV infusion every 3 weeks +Inj.Carboplatin 400 mg/m2 IV infusion every 4 weeks.

All the patients were females in the age group of 25-70 years.

AGE DISTRIBUTION

Table 1: Age Distribution of patients

S.No	AGE(Yrs)	No of Patients	% of patients
1.	30	4	6.7%
2.	31-40	16	26.7%
3.	41-50	22	36.7%
4.	51-60	11	18.3%
5.	61-70	7	11.7%

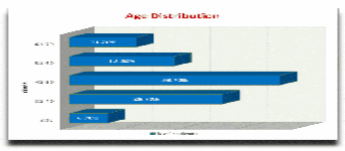

Table 1& Figure 1 show the age distribution of the breast cancer patients. 6.7% of patients were in age group 30 years, 26.7% in age group 31-40 years, 36.7% in age group of 41-50 years, 18.3% in age group 51-60 years & 11.7% in age group 61-70 years. More Patients were in the age group 41-50 years followed by 31-40 years**.**

SEX DISTRIBUTION: All the 60 patients were females

MARITAL STATUS

Table 2: Marital Status of Breast Cancer Patients

S.NO	MARITAL STATUS	No of PATIENTS (n=60)	% of PATIENTS
1.	Married	49	81.7%
2.	Unmarried	11	18.3%

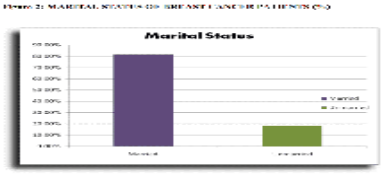

Table 2& Figure 2 shows the marital status in patients with breast cancer with more patients were found to be married about 81.7% followed by 18.3% unmarried.

STAGES OF BREAST CANCER – DISTRIBUTION

Table 3: Stages of Breast Cancer

S.NO	STAGES OF BREAST CANCER	No of PATIENTS (n=60)	% of PATIENTS
1.	II	15	25%
2	III	32	53.3%
3.	IV	13	21.7%

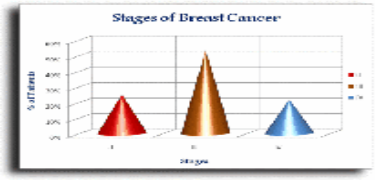

Table 3 & Figure 3 show the distribution of breast cancer patients in Stages II, III and IV. More patients (53.3%) were in stage III followed by stage II (25%).

PATTERN OF ADVERSE EFFECTS

Table 4: Pattern of Adverse Effects

ADVERSE EFFECTS	REGIMEN (no of patients)			TOTAL No of PATIENTS (n= 60)	% OF PATIENTS
	I (n=26)	II (n=19)	III (n=15)		
Nausea/Vomiting	18	14	10	42	70%
Mucositis	15	9	7	31	51.7%
Anemia	14	6	7	27	45%
Thrombocytopenia	0	6	7	13	21.7%
Tingling& Numbness	5	6	3	14	23.3%
Alopecia	12	7	5	24	40%
Diarrhoea	5	4	2	11	18.3%
ECG changes	3	0	0	3	5%
Hematuria	2	0	0	2	3%
Elevated AST/ALT	4	0	0	4	6.7%
Allergic reactions	1	4	2	7	11.7%
Arthralgia	0	1	4	5	8.3%

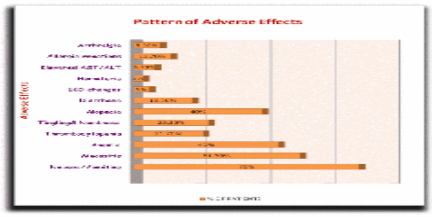

Table 4 & Figure 4 show the pattern of adverse effects in patients with cancer breast. Out of 60 patients receiving 3 regimen of these drugs, the adverse effects reported in % were as follows: nausea/vomiting (70%), mucositis (51.7%), anemia (45%), thrombocytopenia(21.7%),tingling & numbness(23.3%),alopecia (40%), diarrhoea(18.3%),ECG changes (5%), hematuria (3%) ,elevated AST/ALT (6.7%),allergic reactions (11.7%),arthralgia (8.3%). Most common adverse effect observed was nausea/vomiting. Next to it were mucositis, anemia, alopecia, thrombocytopenia, tingling & numbness.

CAUSALITY ASSESSMENT

Table 5: Causality assessment of adverse drug reactions

ASSESSMENT CATEGORY	No. of Patients	% of Patients
	(n=60)	
CERTAIN	0	0
PROBABLE	2	3.7%
POSSIBLE	52	96.3%
Total	54	100%

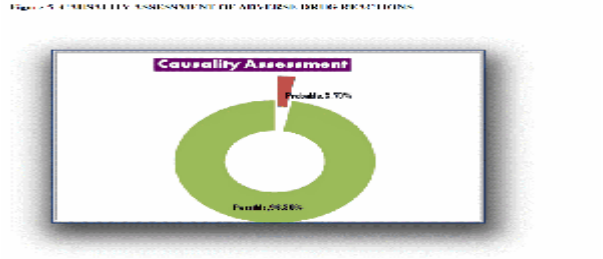

Table 5 & Figure 5 show the Causality assessment of ADR. Causality assessment according to Naranjo's algorithm, 52 (96.3%) ADRs falls under possible category and 2(3.7%) ADRs fall under probable category. Hematuria (2) was found to be probable while other adverse effects (54) were found to be possible.

SEVERITY ASSESSMENT

Table 6: Severity assessment of adverse drug reactions

ASSESSMENT CATEGORY	No. of Patients	% of Patients
MILD	52	96.3%
MODERATE	2	3.7%
SEVERE	0	0
Total	54	100%

Table 6 & Figure 6 show the Severity assessment of ADRs. Severity assessment according to Modified Hartwig Siegel Scale, showed that most of the ADRs (52(96.3%)) fall under mild category and 2(3.7%) fall under moderate category. Discontinuation of the drug was needed in 2 cases (hematuria), Mesna has been given to correct it. None of the ADRs were severe or life threatening. Table 6 & Figure 6 show the Severity assessment of ADRs. Severity assessment according to Modified Hartwig Siegel Scale, showed that most of the ADRs (52(96.3%)) fall under mild category and 2(3.7%) fall under moderate category. Discontinuation of the drug was needed in 2 cases (hematuria), Mesna has been given to correct it. None of the ADRs were severe or life threatening.

DISCUSSION

Our study observed the pattern of ADRs caused by anti cancer agents used in patients with breast cancer in a tertiary care teaching hospital - Govt. Stanley Medical College, Chennai. In our study, out of 60 breast cancer patients who were receiving various combinations of anti cancer drugs 54(90%) patients developed ADRs. All the 60 patients were females. They belong to age group 41-50 years predominantly, followed by 31-40 years. Among them, 49(81.7%) were married and 11(18.3%) were unmarried. In this study, 32 (53.3%) patients belong to Stage III cancer followed by 15(25%) & 13 (21.7%) patients in stage II & IV respectively. For stage II & III cancer chemotherapy were administered in multidrug combinations as neoadjuvant chemotherapy. Stage IV it was administered as palliative management. They were treated with three types of regimens, namely Doxorubicin+ 5FU+ Cyclophosphamide (**Group I**), Gemcitabine +Etoposide (**GroupII**), Paclitaxel+Carboplatin (**GroupIII**) in Dept of Oncology, Govt. Stanley Medical College. Nausea/vomiting was found to be more predominant compared to other adverse effects. In other studies also this was the predominant ADRs(7). Next to it was mucositis, anemia, alopecia, thrombocytopenia and tingling & numbness. Least is diarrhoea, allergic reactions, arthralgia, ECG changes, elevated liver enzymes and hematuria. Nausea and vomiting are prominent with many cytotoxic drugs. This is due to direct stimulation of CTZ(8) by the drug, as well as generation of emetic impulses/mediators from the upper GIT. High emetogenic potential is seen with Cyclophosphamide. Moderate emesis is seen in Carboplatin, Doxorubicin and Paclitaxel. Mild emesis is seen in Etoposide & Gemcitabine. The use of antiemetic agents (ondansetron) as premedication has significantly decreased the incidence of nausea and vomiting . Next to it was mucositis/ stomatitis.

The oral mucosa is particularly susceptible to cytotoxic drus because of high epithelial turnover. The chemotherapeutic drugs like 5FU, Doxorubicin(10), Cyclophosphamide, Paclitaxel produce mucositis/stomatitis as an early manifestation of toxicity; other drugs produce it as later signs. The gums and oral mucosa are regularly subjected to minor trauma, and breaches are common during chewing. Depression of bone marrow results in thrombocytopenia, anemia, granulocytopenia and agranulocytosis. This is the most serious toxicity which might limit the dose that can be employed. Anaemia due to chemotherapy induced myelosuppression usually occurs 2-3 weeks after the administration of chemotherapy and can be managed by blood transfusion and erythropoietin (9). The dose limiting toxicity for Carboplatin is thrombocytopenia (10) , Cyclophosphamide is immuno & myelosupression and for 5FU, Paclitaxel, Doxorubicin, Etoposide & Gemcitabine is myelosupression. The marrow depression is mostly reversible. Infections & bleeding are the usual complications. Alopecia occurs due to damage to the cells in hair follicles. The drugs like 5 FU, Doxorubicin, Paclitaxel and Etoposide more prone to cause alopecia. The anticancer antibiotic Doxorubicin produces dose related cardiotoxicity as an unique adverse effect. This can manifest as ECG changes, arrhythmia, hypotension all of which are reversible. Diarrhoea, shedding of mucosa, hemorrhage occurs due to decrease in the rate of renewal of gastrointestinal mucous lining. 5FU, Gemcitabine, Etoposide are more prone to cause diarrhoea compared to other drugs. Cyclophosphamide and Carboplatin causes elevated liver enzymes but is mild. Hematuria is mainly seen in patients

taking Cyclophosphamide due to hemorrhagic cystitis caused by its toxic vasicotoxic metabolite acrolein. To prevent the same *MESNA* (10) is usually given, as it binds & inactivates this metabolite. Hypersensitivity reactions are mainly seen in Etoposide, Paclitaxel and Carboplatin but are mild which can be treated by antihistaminics, glucocorticids(10). Peripheral neuropathy is seen most commonly in Paclitaxel, 5FU, Carboplatin and Gemcitabine as dose limiting toxicity. Arthralgia/myalgia is found to be common in Paclitaxel than other drugs. Causality assessment according to Naranjo's algorithm shows 96.3% ADRs were possible,3.7% ADRs were probable.Severity assessment according to Modified Hartwig Siegel scale shows most of the ADRs were mild (96.7%) and only 2(3.7%) patients with hematuria observed to be moderate for whom Mesna has been given for the same. Since Pharmacovigilance is gaining importance all over the country, this study will bring awareness of adverse effects due to anticancer drugs used in patients with breast cancer. Some of the adverse effects needs dosage modification or discontinuation or change the offending drug. Routine adverse drug reactions monitoring is needed for early detection of those adverse effects & treatment modification, thereby it helps in reducing patient's suffering & improving quality of life.

CONCLUSION

The anticancer drug combinations used in our institution were Doxorubicin+5FU+ Cyclophosphamide, Gemcitabine+Etoposide & Paclitaxel+Carboplatin. These drugs were associated with varied adverse effects. The adverse event prevalence encountered suggests that practically all patients receiving cytotoxic drugs suffer one or more AEs. So, early detection of drug toxicity may help in modifying the doses and premedication can be given to minimize the toxic effects. Further outgrowth of the study will help us to document the adverse effects which may go unrecognized.

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