A RETROSPECTIVE AND PROSPECTIVE STUDY FOR ADVERSE DRUG REACTION OF CANCER CHEMOTHERAPY IN BREAST CANCER
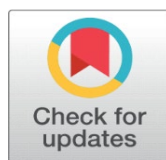
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ABSTRACT

Cancer is the major health problem worldwide, according to WHO in 2018 cancer is responsible for an estimated 9.6 mill death out of 18.1 million new cases and globally 6 deaths occur due to cancer. Cancer is the abnormal, unwanted growth of cells, when abnormal cells divide in an uncontrolled way within the body and destroy normal tissue that can lead to death. Normal body cell grows, divide, and die in an orderly way or cancer cells are different because they do not die, grow continuously, and divide in orderly way. There are more than 200 types of cancer. Any agent that converts a body cell to develop abnormally can cause cancer. The cancer causative agents include- radiations, chemical or toxic compound exposure, lifestyle, hormones, and human genetics. Most tumors can be categorized as one of the three main groups: carcinomas, sarcomas and leukemia or lymphomas. Carcinomas, which associated around 90% of human cancer, are malignancies of epithelial cell. Sarcomas, which are uncommon in human, are solid tumor of connective tissue including muscle, bone, cartilage, and fibrous tissue. Leukemia and lymphomas, which represent around 8% of human malignancies, emerge from the blood forming cell and from cell of immune system. Carcinoma of breast is a malignant disease with variable outcomes. Breast carcinoma is second most common cause of death in females though it can also occur in men but are very uncommon. This type of cancer is malignant cell growth in breast. This study was done to compare and analyze adverse drug reactions of cancer chemotherapy in breast cancer in a rural hospital. Objectives included- a) To study adverse drug reactions of various chemotherapeutic agents used in patients suffering breast cancer b) To compare various side-effects as a result of different combination protocols to identify the drug protocol with least amounts of adverse drug reactions. However, an extremely significant difference was found between all of the comparison groups studied.

Keywords: Breast Cancer, Carcinomas, Sarcomas, Leukemia, Lymphomas, Women

1. INTRODUCTION

The incidence of breast cancer increasing day by day in India. Breast cancer is second most frequent cause of death among women. Breast cancer also occurs in men but it's very far less common. In this type of condition, cancer may be present as a lump or nipple discharge Sharma et al. (2010) Most of the breast cancers are adenocarcinomas which arise from glandular tissue and there are about 30 different subtypes of adenocarcinoma.

Adenocarcinoma is a type of cancer affecting glands. In case of breast cancer adenocarcinoma starts from the glands of breast where milk produce.

2. TYPES OF BREAST CANCER

Adenocarcenoma is categorized in two parts –

1) Ductal carcinoma in situ
2) Lobular carcinoma in situ

These are the form of breast cancer. In Ductal carcinoma in situ abnormal cell are present but still contained in the milk duct. Lobular carcinoma in situ is found in the breast lobules but not yet surrounding tissue.

3. OTHER COMMON TYPES OF BREAST CANCER

- Inflammatory breast cancer
- Medullary breast cancer
- Paget disease of the breast
- Papillary breast carcinoma
- Invasive ductal carcinoma

1) **Lobular carcinoma in situ** This type of cancer develops in the milk glands (lobules) of the breast. Lobule is a gland that produces milk.

The term "In Situ" refers that the abnormal cells are present in the same place where they first formed or they have not spread. The lobules of the breast's exterior have not been affected by LCIS.

2) **Ductal cancer in situ** In DCIS the abnormal cells present inside the milk duct in the breast. Both LCIS & DCIS identified non breast cancer that has spread.

When aberrant cells within the milk duct or lobules burst and infiltrate the surrounding tissue, invasive breast cancer is the result. Cancer cells spread throughout the body from the breast to other areas via the systemic circulation.

The most common invasive breast cancer includes:

1) **Invasive ductal carcinoma** that begin in the milk duct
2) **Invasive lobular carcinoma** that begin in the lobules.
3) **Breast cancer that is inflammatory** results from cancer cells obstructing lymphatic arteries or channels in the skin above the breast. The breast seems enlarged, red, and inflamed; this is why it is called an inflammatory condition.
4) **Paget disease in the breast** This extremely uncommon type of breast cancer begins on the nipple and spreads to the area around the nipple. About 1-4.3% of all breast cancer cases were this form of malignancy. It is connected to underlying ductal carcinoma, either invasive or in situ.

4. ETIOLOGY AND RISK FACTOR

A risk factor is anything that increases the risk of breast cancer. The risk factor of breast cancer is unknown, many women who suffer breast cancer have no known

factor like simple being women. The studies suggest that the main risk factor that is associated with an increase risk of breast cancer include:

1) Studies show that the main risk factor of breast cancer includes being women. Breast cancer develops in women more likely than men.

2) **Age** Breast cancer is increasing with age, most breast cancer is diagnosed after age 50 year.

3) **Family History** A women have higher risk if she has a first degree relative or multiple relative family member affect by breast cancer.

4) **Drinking Alcohol** Studies show that the women's risk is increases with drinks more alcohol.

5) **Radiation therapy** If you received radiation therapy as a child or young, the risk of breast cancer is increases.

6) **Hormonal factors** the women who take hormone therapy (include estrogen and progesterone) during menopause can raise the risk for breast cancer.

7) **Heredity** Breast cancer development is a complex process involving mutational and genetic event. Gene wide association's studies suggest that multiple mutations are present in breast cancer and more than 20 mutations identified, each of which impart a small increase in frequency of breast cancer. The most common mutation includes BRCA1and BRCA 2 genes that are associated with approximately 5%of breast cases.

8) **Obesity** The studies suggest that the dietary fat increase the risk of breast cancer. Intake high calories lead to weight gain and obesity. Obesity increases the risk of breast cancer because obese women may have an increased exposure of breast tissue to estrogen that results hyper estrogenic state. Mansfield (1993)

5. SIGN AND SYMPTOMS OF BREAST CANCER

The sign and symptoms of breast cancer are depending upon the type of breast cancer. Different types of breast cancer produce varieties of symptoms some of which may be common while others may be different. The most common sign &symptoms of breast cancer may include: Ames et al. (1995)

- The size shape or appearance of a breast is change.
- The most common sign of breast cancer is a lump or thickening in the breast that feel different from the surrounding tissue.
- Skin over the breast is change, such as dimpling.
- Nipple discharge
- Change in the breast color.
- Peeling or flaking of skin surrounding nipple.
- Redness, swelling, itching and rashes on the breast.
- Change the shape of nipple.

6. SCREENING

Screening can be done to detect breast cancer as soon as possible to provide better treatment. Many screening programs have been intended to detect small, early cancer. The breast cancer screening can be done with Mammography and

other clinical examination like ultrasound and MRI. The mortality is decrease with mammography screening and a report of randomized control trial show the 31 % mortality is decrease. Women aged 40 or above required a routine screening programmed at every 1to 2 year, whether or not symptoms are clear. Berry et al. (2005)

7. TREATMENT

There are different treatments approaches of breast cancer, treatment depend upon the type and size of tumor. The main treatment of breast cancer is surgery, chemotherapy, radiotherapy, and hormone therapy. In surgery mostly modified redical mastectomy, simple mastectomy and quadrantectomy are done. Post operative chemotherapy is given after surgery in all cases. In radiation therapy a beam of energy is designed to kill breast cancer. Radiation therapy can be used before the surgery to shrink large tumor or after surgery to kill remaining breast cancer cell. Radiation therapy can be given surrounding the area where cancer is present. Cameron et al. (1994), Arruebo et al. (2011).

8. REVIEW OF LITERATURE
8.1. DOXORUBICIN

It is an antibiotic from Anthracycline family used in the treatment of cancer including breast, lungs, gastric, ovarian, thyroid, sarcoma, pediatric cancer etc.

1) Thorn et al. (2011): Doxorubicin inhibits topoisomerase II which is responsible for DNA synthesis. Doxorubicin inhibits macromolecular production by intercalating into DNA. The anticancer chemical used in Dox-based chemotherapy affects healthy tissue, causing toxicity and adverse effects, and does not only target breast cancer.

    Cardiotoxicity is the primary hazardous consequence, and usage of the substance can result in the development of cardiomyopathy, which can progress to biventricular failure and even death. Acute toxicities of Doxorubicin include nausea, vomiting, myelosuppression, alopecia and mucositis. Myelosupression is the acute dose limiting toxicity wherein the WBC.

2) Zoli et al. (n.d.) reported that Doxorubicin and paclitaxel in combination show synergistic cytocidal effects. After the sequence of Dox-Pacl apoptosis was observed.

3) Luikart et al. 1984: A combination of AVM (Doxorubicin, Vinblastin & Mitomycin) the major toxicity was myelosuppression. In some cases leucopenia, thrombocytopenia and anemia was found. One patient receives CMF (cyclophosphamide, methotrexate & 5-flurouracil) developed acute myelogenous leukemia after starting AVM.

4) Zhao et al. 2017: The most important side effects of pegylated liposomal doxorubicin in adjuvant chemotherapy for breast cancer were skin toxicity, stomatitis and hand-foot syndrome.

5) Song et al. (2011): Anthracyclines based regimens have been the backbone in adjuvant chemotherapy. These are cardiotoxic and makes serious and irreversible damage on heart. Studies show that congestive heart failure is the main risk of higher dose of doxorubicin.

8.2. CYCLOPHOSPHAMIDE

Cyclophosphamide is nitrogen mustard alkylating agent used in different type of cancer including breast cancer. It inhibits DNA, RNA, and protein synthesis by acting on cross linking purine base in DNA. Toxic effects of cyclophosphamide include bone marrow suppression, cardiotoxicity and hemorrhagic sistitis. Cardiotoxicity may occur when very high dose are given. Common side effects are nausea and vomiting which is well controlled by antiemetic drugs.

1) Song et al. (2011): The main toxic effects of TC (Docetaxel &cyclophosphamide) regimen were neutropenia and common non hematological toxicity developed in patients was hair loss, fatigue, nausea, and vomiting. Other side effects include constipation, peripheral neuropathy, and hyperglycaemia in some cases.

2) North R. J. 1982: Cyclophosphamide is used in breast and ovarian cancer at much lower doses as a single agent or as adjuvant treatment for treat lymphomas. The effectiveness of low dose of cyclophosphamide is essentially because of its capacity to promote antitumor immunity by selective depletion of regulatory T cell and enhancement of effectors T cell functions.

3) Castel et al. (2013): Congestive Heart failure is the most serious cardiac complication due to cyclophosphamide at high dose. Other common side effects include hypotension, hypertension, arrhythmias and conduction disturbances, pericarditis, and thromboembolic complications.

4) Karisson Y. A. et al. (1998): In a study report of 128 Patients in the treatment of advanced breast cancer with FEC (5-flurouracil, epirubicin and cyclophosphamide) regimen, no cardiac failure or toxic death were recorded. The common toxicities alopecia and nausea were observed.

9. METHODOLOGY

Cases undergoing chemotherapy for breast cancer were included and patients had to be above 18 years of age.

Inclusion criteria were-

1) Adjuvant chemotherapy
2) Palliative chemotherapy in advance cases

Exclusion criteria-

1) Pregnant women
2) Neonates

10. DOSES USED IN THIS STUDY
10.1. IN THIS STUDY DIFFERENT TYPE'S COMBINATION CHEMOTHERAPY PROTOCOL ARE USED

- CAF: Cyclophosphamide 600-1000mg/m2+ Doxorubicin 60-75mg/m2+ 5-Flurouracil 500mg/m2
- FMC: 5-Flurouracil 500mg/m2 + Methotrexate 40-80mg/m2 + Cyclophosphamide 600- 1000mg/m2

- DC: Docetaxel 60-100mg/m2 + carboplatin 250mg/m2 PC: Paclitaxel 135-225mg/m2 + cisplatin 40-120mg/m2. Shewach and Kuchta (2009)

10.2. CALCULATION OF BODY SURFACE AREA

Direct measurements is difficult so various formulae is used to calculate the Body Surface area (BSA) which is used in many measurements in medicine including the calculation of drug dosages and the amount of fluid to be administered IV. Some formulae are listed below:

1) Du Bois formula: BSA = 0.007184 X W0.425 X H0.725
2) Mosteller formula: BSA = 0.016667 X W0.5 H0.5
3) Haycock formula: BSA = 0.0235 X W0.5378 X H0.3964
4) Gehan and George formula: BSA = 0.0235 X W0.51456 X H0.42246
5) Boyd formula: BSA = 0.03330 X W(0.6157-0.0188 X LOG 10(W) X H0.3
6) Fujimoto formula: BSA = 0.008883 X W 0.444 X H 0.663
7) Takahira formula: BSA = 0.007241 X W 0.425 X H 0.725
8) Shlich formula: BSA = 0.000975482 X W 0.46 X H 1.08 (Women) BSA = 0.000579479 X W 0.38 X H 1.24 (Men)

NOTE: In this study Du Bois formula has been used.

11. DOSE CALCULATION

Drug doses are calculated according to the patient's body surface area and occasionally, by height. For this study, accurate weight was used for great consistency of drug dosing.

Side effects observed in this study

1) Nausea
2) Vomiting
3) Diarrhea
4) Alopecia
5) Weight loss
6) Stomatitis
7) Constipation
8) Palpitation
9) Cardiotoxicity
10) Neutropenia
11) Loss of appetite
12) Fever
13) Skin rashes
14) Thrombocytopenia
15) Shock
16) Nail blackening
17) Leukopenia
18) Neuropathy
19) Inflammation

20) Anemia

21) Haematuria

22) Hyperacidity

23) Depression

24) Mood swing

Table 1

Table 1 Table Showing Combination Chemotherapy Protocol Used in this Study			
S. No	Protocol used	NO of patients	% of Patients
1	CMF	10	25
2	FAC	10	25
3	DC	10	25
4	PC	10	25

12. RESULT AND OBSERVATIONS

Table 2

Table 2 Table Showing Gender Distribution			
S. No	Sex	Number of Patient	Percentage
1	Male	0	0%
2	Female	40	100%

Table 3

Table 3 Table Showing Chances of Disease Occurrence on the Basis of Age			
S. No	Age in Year	No. of Patient	Percentage
1	20 – 25	0	0%
2	26 – 30	1	2.5%
3	31 – 35	2	5%
4	36 – 40	2	5%
5	41 – 45	9	22.5%
6	46 – 50	10	25%
7	51 – 55	7	17.5%
8	56 – 60	5	12.5%
9	61 – 65	3	7.5%
10	66 – 70	1	2.5%
11	70 above	0	0%

Table 4

Table 4 Side Effects Seen in Cyclophosphamide, Methotrexate & 5-FU Protocol			
S. No	Side effects	No of Patient	Percentage
1	Nausea	10	100%
2	Vomiting	10	100%
3	Alopecia	9	90%
4	Loss of appetite	8	80%
5	Weight loss	6	60%
6	Stomatitis	3	30%
7	Constipation	1	10%
8	Palpitation	1	10%
9	Anorexia	3	30%
10	Neutropenia	4	40%
11	Diarrhea	7	70%
12	Mood swing	2	20%
13	Skin rashes	1	10%
14	Fever	3	30%

S. No	Side effects	No of Patient	Percentage
15	Leukopenia	3	30%
16	Thrombocytopenia	1	10%
17	Mettalic taste	3	30%
18	Insomnia	2	20%
19	Weakness	6	60%
20	Neuropathy	1	10%
21	Inflammation	2	20%
22	Anemia	3	30%
23	Haematuria	1	10%
24	Shock	2	20%
25	Nail blackening	1	10%
26	Hyperacidity	5	50%

Table 5

Table 5 Side Effects Seen In 5-FU, Doxorubicin and Cyclophosphamide Protocol			
S. No	Side effects	No of Patient	Percentage
1	Nausea	10	100%
2	Vomiting	10	100%
3	Diarrhea	6	60%
4	Alopecia	8	80%
5	Weight loss	7	50%
6	Stomatitis	4	60%
7	Shock	1	60%
8	Palpitation	2	40%
9	Cardiotoxicity	1	10%
10	Thrombocytopenia	3	20%
11	Loss of appetite	6	60%
12	Fever	4	40%
13	Anorexia	2	60%
14	Netropenia	5	60%
15	Leukopenia	2	30%
16	Skin rashes	3	50%
17	Mettalic taste	3	55%
18	Insomnia	3	45%
19	Weakness	5	45%
20	Neuropathy	2	7.5%
21	Inflammation	1	5%
22	Anemia	2	10%
23	Haematuria	2	7.5%
24	Hyperacidity	6	50%

25	Depression	2	30%
26	Mood swing	1	20%
27	Chest pain	1	7.5%

Table 6

Table 6 Side Effects in Docetaxel and Carboplatin Protocol			
S. No	Side effects	No of Patient	Percentage
1	Nausea	10	100%
2	Vomiting	10	100%
3	Diarrhea	6	60%
4	Alopecia	3	30%
5	Weight loss	5	50%
6	Stomatitis	3	30%
7	Constipation	1	10%
8	Palpitation	1	10%
9	Cardiotoxicty	2	20%
10	Shock	1	20%
11	Loss of appetite	5	50%
12	Fever	4	40%
13	Skin rashes	2	20%
14	Neutropenia	3	30%
15	Leukopenia	1	10%
16	Thrombocytopenia	1	10%
17	Mettalic taste	2	20%
18	Insomnia	2	20%
19	Weakness	7	70%
20	Neuropathy	1	10%
21	Inflammation	1	10%
22	Anemia	1	10%
23	Haematuria	1	10%
24	Hyperacidity	4	40%
25	Depression	1	10%
26	Anorexia	1	10%

Table 7

Table 7 Side Effects Seen in Paclitaxel and Cisplatin Protocol			
S. No	Side effects	No of Patient	Percentage
1	Nausea	10	100%
2	Vomiting	10	100%

3	Diarrhea	5	50%
4	Alopecia	4	40%
5	Weight loss	5	50%
6	Stomatitis	2	20%
7	Weakness	5	50%
8	Palpitation	2	20%
9	Cardiotoxicty	1	10%
10	Leucopenia	2	20%
11	Loss of appetite	6	60%
12	Fever	2	20%
13	Skin rashes	1	10%
14	Thrombocytopenia	2	20%
15	Hyperacidity	5	50%
16	Mood swing	1	10%
17	Mettalic taste	3	30%
18	Insomnia	1	1%
19	Anorexia	1	1%
20	Neuropathy	3	3%
21	Inflammation	2	2%
22	Anemia	2	20%
23	Neutropenia	4	40%
24	Nail blacknening	1	10%

Table 8

Table 8 According to Side Effects Distribution			
S. No	Side effects	No. of Patient	Percentage
1	Nausea	40	100%
2	Vomiting	40	100%
3	Diarrhea	24	60%
4	Alopecia	24	60%
5	Weight loss	23	57.5%
6	Stomatitis	12	30%
7	Constipation	2	5%
8	Palpitation	6	15%
9	Cardiotoxicty	4	10%
10	Neutropenia	16	40%
11	Loss of appetite	25	62.5%
12	Fever	13	32.5%
13	Skin rashes	6	15%
14	Thrombocytopenia	7	17.5%

15	Shock	4	10%
16	Nail blackening	2	5%
17	Leukopenia	8	20%
18	Mettalic taste	11	27.5%
19	Insomnia	8	20%
20	Weakness	23	57.5%
21	Neuropathy	7	17.5%
22	Inflammation	6	15%
23	Anemia	8	20%
24	Haematuria	4	10%
25	Hyperacidity	20	50%
26	Depression	3	7.5%
27	Mood swing	4	10%
28	Chest pain	1	2.5%
29	Anorexia	7	17.5%

Table 9

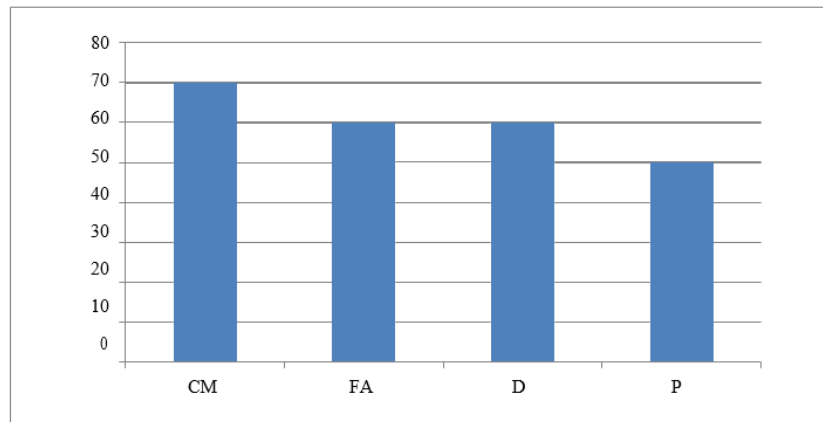| **Table 9 Percentage of Patients Showing ADR-Vomiting**			
S. No	**Drug regimen**	**No of Patient**	**Percentage**
1	CMF	10	100%
2	FAC	10	100%
3	DC	10	100%
4	PC	10	100%

Graph 1
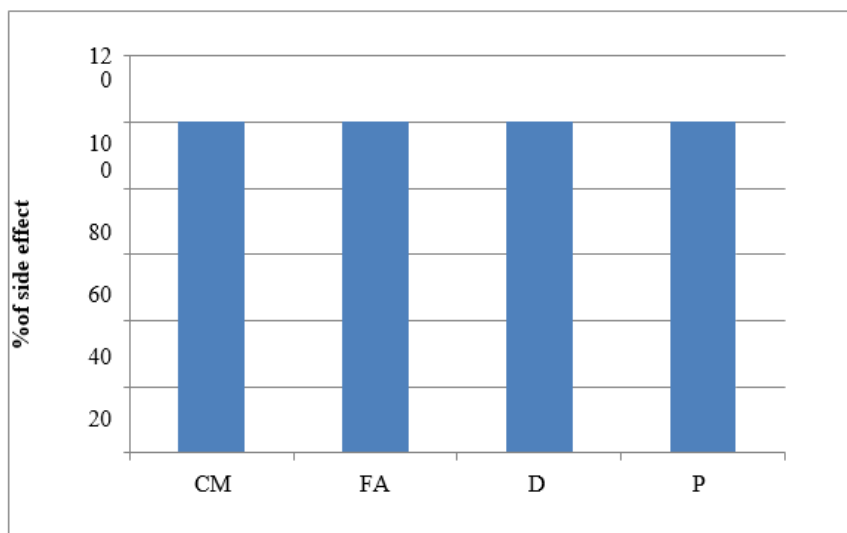
Graph 1 Graph Showing ADR –Vomiting
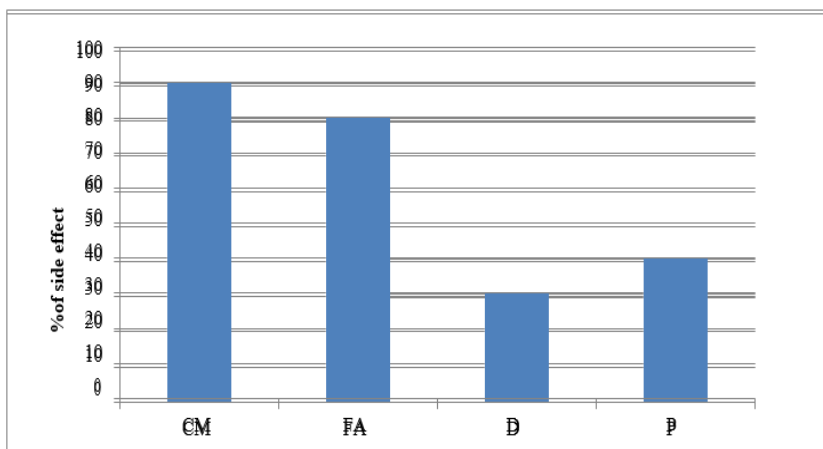
Graph 2
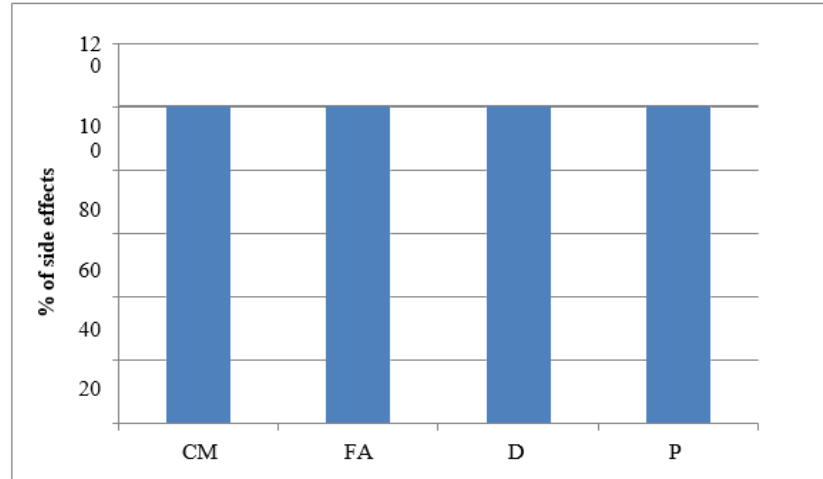
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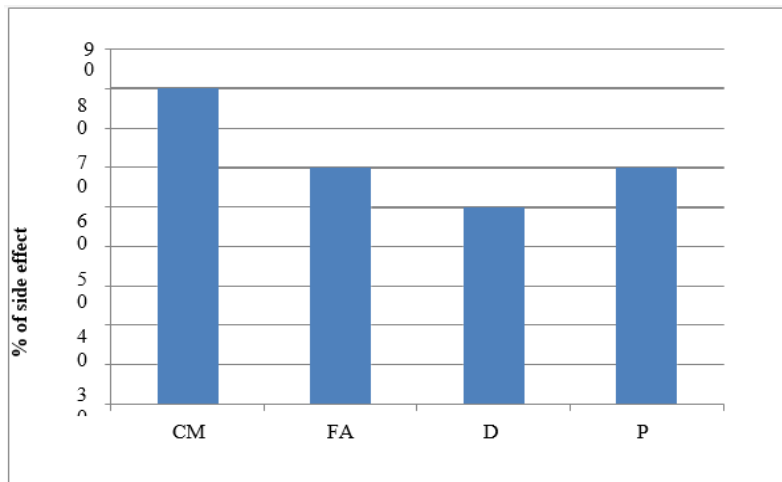
Graph 3

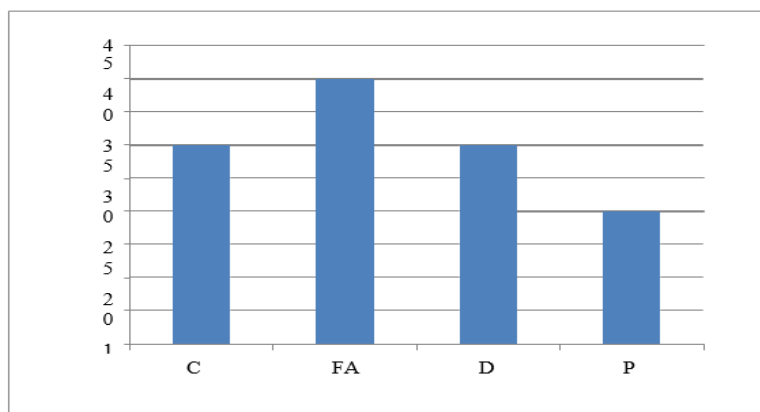**Graph 3** Graph Showing ADR – Diarrhea

Graph 4

Graph 4 Graph Showing ADR –Alopecia
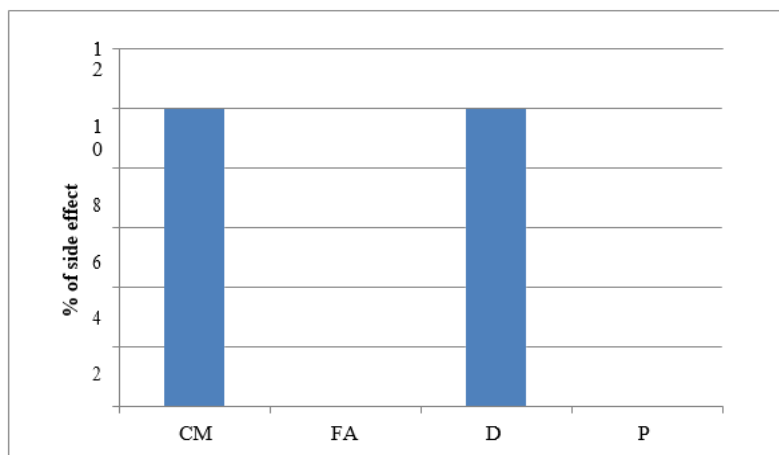
Graph 5

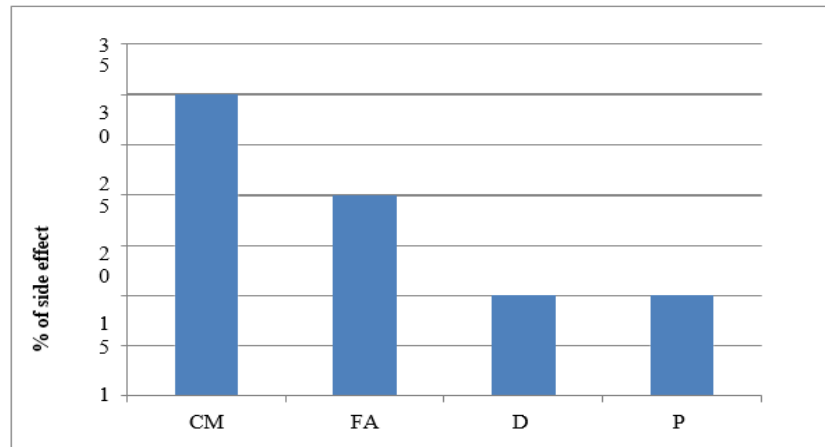**Graph 5** Graph Showing ADR –Loss of Appetite

Graph 6

Graph 6 Graph Showing ADR –Stomatitis

Graph 7

Graph 7 Graph Showing ADR –Constipation

Graph 8

Graph 8 Graph Showing ADR –Anorexia

Table 10

Table 10 Table Demonstrating Studied Adverse Drug Reactions with Statistical Significance

Adverse drug reaction	P value
Vomiting	<0.0001
Nausea	<0.0001
Diarrhea	<0.0001
Alopecia	<0.0001
Loss of appetite	<0.0001
Stomatitis	<0.0001
Constipation	<0.0001
Weight loss	<0.0001
Palpitation	<0.0001
Skin rashes	<0.0001
Neutropenia	<0.0001
Cardiotoxicity	<0.0001
Fever	<0.0001
Thrombocytopenia	<0.0001
Leucopenia	<0.0001
Metallic taste	<0.0001
Insomnia	<0.0001
Weakness	<0.0001
Shock	<0.0001
Nail blackening	<0.0001
Neuropathy	<0.0001
Inflammation at injection site	<0.0001

Anemia	<0.0001
Hematuria	<0.0001
Hyperacidity	<0.0001
Depression	<0.0001
Chest pain	<0.0001
Mood swings	<0.0001
Anorexia	<0.0001

13. STATISTICAL ANALYSIS

Unpaired T test was employed as statistical tool and significance was determined based on P values i.e., P<0.5 – significant; <0.001- highly significant and <0.0001- extremely significant.

14. CONCLUSION

Highest case of breast cancer was found in 41 to 45 year of age group. Nausea and vomiting resulted from all the studied drug protocols used for treating breast cancer. The cyclophosphamide- methotrexate and 5- fluorouracil drugs protocol showed maximum case of alopecia (in 90% patients) followed in decreasing order as follows- appetite loss (80%), diarrhea (70%), weight loss (60%), hyperacidity (50%), neutropenia (40%), anemia, leucopenia, stomatitis, anorexia, and metallic taste (30%), skin rashes, nail blackening (10%).

The 5- fluorouracil- doxorubicin and cyclophosphamide protocol presented with alopecia (80%) followed by- diarrhea, stomatitis, shock, appetite loss, anorexia and neutropenia (60%), hyperacidity, weight loss and skin rashes (50%), insomnia and weakness (45%), palpitation (40%), metallic taste and depression (30%), mood swings (20%). Chest pain, hematuria and neuropathy (7.5% cases). In Docetaxel and carboplatin protocol, diarrhea was most common adverse effect (60%) which was followed by – weight loss and loss of appetite (50%), fever (40%), stomatitis, alopecia, and neutropenia in 30% cases. In the Paclitaxel and cisplatin protocol, loss of appetite was seen in 60% cases followed by diarrhea, weakness and hyperacidity in 50% and alopecia and neutropenia in 40% cases. All study group showed extremely significant differences (P<0.0001) between the adverse drug reaction studied.

CONFLICT OF INTERESTS

None.

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