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Chemotherapy Regimen And Toxicity Profile In Patient Receiving Systematic Treatment For Breast Cancer

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ABSTRACT: Breast cancer originates in your breast tissue. It occurs when breast cells mutate (change) and grow out of control, creating a mass of tissue (tumor). Like other cancers, breast cancer can invade and grow into the tissue surrounding your breast. It can also travel to other parts of your body and form new tumors. When this happens, it's called metastasis.

OBJECTIVE: The primary goal of the study is to assess the prescription pattern of chemotherapy regimen for breast cancer.

The secondary goal of the study is to assess post chemotherapeutic toxicities in patient with breast cancer.

To compare haematological and non - haematological toxicities in women with breast cancer.

METHODOLOGY: It was a prospective observational study; a sample size of 60 patients prescription details was checked, potential ADR and drug-drug interactions were assessed. Another aspect of the study is to look at the clinical effectiveness and the side effects encountered by the patients.

RESULTS: The clinical data of 60 patients were assessed; among them 60 patients was female. The age group that was more affected was from 50-59(50%) of patients It was observed to occur commonly in left breast 41 patients (68%). Breast cancer hormone receptor estrogen that the number of patients with positive ER are 24, in the percentage of (41%) and number of patients with negative ER are 35, in the percentage of (59%). patients with positive PR are 20, in the percentage of (33%) and number of patients with negative PR are 40, in the percentage of (67%). Patients with positive HER2 are 10, in the percentage of (17%) and number of patients with negative HER2 are 50, in the percentage of (83%). The number of patients with triple negative breast cancer are 22, in the percentage of (37%) and number of patients with triple positive breast cancer are 0, in the percentage of (0%).

Breast cancer staging in which the third stage 53% is the highest followed by fourth 28% and second stage 18%.

Identification of TNM in which pathological identification is dominant over clinical identification. Among these anticancer drugs, Cyclophosphamide is used by 43 patients accounting to 72%, and hence is a dominating choice of drug. Doxorubicin on the other hand is used by 31 patients implying 52% of usage. Followed by Paclitaxel used by 23 patients (38%), Carboplatin used by 13 patients (22%), Docetaxel used by 11 patients (18%) and the least usage of drug being of Transtuzumab which is used by 3 patients (5%).

Hematological toxicity observed in patients undergoing chemotherapy shows high risk chances of Anemia with 36 number of patients, yielding to (60%) which is the maximum among all the other toxicities, followed by Neutropenia with 35 number of patients (58%), followed by Leukopenia with 22 number of patients (37%), and the least among them being Myelosuppression with 19 patients (32%). non-hematological toxicity observed in patients undergoing chemotherapy shows alopecia with 51 number of patients, yielding to 85%% which is the maximum among all the other toxicities, followed by Nail discoloration with 46 number of patients (77%), followed by edema lower limb with 37 number of patients(62%), followed by anorexia 34 number of patients (57%), followed by nausea and vomiting and neuropathy with 32 number of patients (53%), followed by joint pain with 31 number of patients (52%), followed by mucositis with 19 number of patients (32%), followed by cardiac toxicity with 5 number of patients(8%) and nephrotoxicity with 4 number of patients(7%).

The interacting drugs and effect of interaction are as below:

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DOXORUBICIN+CYCLOPHOSPHAMIDE-LEADS TO INCREASE RISK OF HEMORRHAGIC CYSTITIS
CARBOPLATIN+DOCETAXEL-LEADS TO INCREASE RISK OF PERIPHERAL NEUROPATHY
CYCLOPHOSPHAMIDE+CARBOPLATIN-MAY RESULT IN ADDITIVE TOXICITIES PARTICULARLY IN THE BONE MARROW AND GASTROINTESTINAL TRACT
CARBOPLATIN+PACLITAXEL-LEADS TO INCREASE RISK OF PERIPHERAL NEUROPATHY
CONCLUSION: In the assessment of current prescribing patterns of chemotherapy regimen,our study raises awareness of the potential ADRs, Identifying and monitoring drug interactions has a significant part in forming a standard therapeutic plan will reduce the occurance of adverse events and their severity in hospitalized patients and suggests prescribers about alternatives to reduce the adverse events.
KEYWORDS: BC, ER, PR, HER2, TNM, TNBC
ABBREVIATION: BC-Breast cancer, ER-Estrogen receptor, PR- Progesterone receptor, HER2- Human epidermal growth factor receptor 2, TNM- Tumor Node Metastatic,
TNBC- Triple negative breast cancer

I. INTRODUCTION

Breast cancer begins when healthy breast cells change and grow out of control, usually forming a mass called a tumor. Breast cancer is the most common type of cancer diagnosed in women. Men can also develop breast cancer, but it is rare. Breast cancer spreads when the cancer grows into adjacent organs or other parts of the body or when breast cancer cells move to other parts of the body through the blood vessels or lymph vessels. This is called a metastasis. BC is the second most prevalent type of cancer worldwide after lung cancer. Approximately 80% of patients present with local or locally advanced disease and undergo resection, followed by adjuvant therapies which may include chemotherapy, endocrine, biologic, or radiation therapy (1).
Additionally, 20-30% of patients who initially present with early breast cancer will acquire a metastatic relapse over time. Whenever the disease reaches a metastatic stage, it remains largely incurable. It has been recognized for a long time that local (only), regional (with spread to nearby lymph nodes), and metastatic (with hematogenous spread to distant organs) cancers have a worsening prognosis. (3,4)
Drug therapies used for breast cancer are classically classified into three categories:

- Endocrine or hormonal therapy
- Targeted therapies, including anti HER2
- Chemotherapy

Breast cancer can be invasive or non-invasive. Invasive breast cancer is cancer that spreads into surrounding are called ductal carcinoma or lobular tissues or distant organs. Non-invasive breast cancer does not go beyond the milk ducts or lobules in the breast. Most breast cancers start in the ducts or lobes and carcinoma:

- **Ductal carcinoma.** These cancers start in the cells lining the milk ducts and make up the majority of breast cancers.
- **Ductal carcinoma in situ (DCIS).** This is a non-invasive cancer that is located only in the duct and has not spread outside the duct.
- **Invasive or infiltrating ductal carcinoma.** This is cancer that has spread outside of the duct.
- **Invasive lobular carcinoma.** This is cancer that started in the lobules and has spread outside of the lobules.

Breast cancer subtypes
There are 3 main subtypes of breast cancer.
Testing the tumor sample can find out if the cancer is:
Hormone receptor positive. Breast cancers expressing estrogen receptors (ER) or progesterone receptors (PR) are called “hormone receptor positive.” These receptors are proteins found in cells. Tumors that have estrogen receptors are called “ER positive.” Tumors that have progesterone receptors are called “PR positive.” Only 1 of these receptors needs to be positive for a cancer to be called hormone receptor positive. This type of cancer may depend on the hormones estrogen or progesterone to grow. Hormone receptor-positive cancers can occur at any age, but are more common in women who have gone through menopause. About two-thirds of breast cancers have estrogen or progesterone receptors. Cancers without these receptors are called “hormone receptor negative.”

HER2 positive. About 20% of breast cancers depend on the gene called human epidermal growth factor receptor 2 (HER2) to grow. These cancers are called “HER2 positive” and have many copies of the HER2 gene or high levels of the HER2

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protein. These proteins are also called "receptors." The HER2 gene makes the HER2 protein, which is found on the cancer cells and is important for tumor cell growth. HER2-positive breast cancers grow more quickly. They can also be either hormone receptor positive or hormone receptor negative. Cancers that have no or low levels of the HER2 protein or few copies of the HER2 gene are called "HER2 negative."

Triple negative. If a tumor does not express ER, PR, and HER2, the tumor is called "triple negative." Triple-negative breast cancer makes up about 15% of invasive breast cancers. Triple-negative breast cancer seems to be more common among younger women, particularly younger Black and Hispanic women. Triple-negative breast cancer is also more common in women with a mutation in the BRCA1 gene. All people with triple-negative breast cancer younger than 60 should be tested for BRCA gene mutations. (10)

TNM Staging

The TNM staging system is used to determine the anatomical extent of malignant disease on the basis of clinical (CTNM) and pathological (PTNM) criteria grouped under three broad headings: the primary tumour (T stage), lymph-node involvement (N stage), and metastasis (M stage). This system was originated more than 50 years ago by Pierre Denoix, has become a worldwide to describe the anatomic extent of cancer and determine its stage; it is therefore the common language of tumor staging. Its application to breast cancer was published 24 years later in 1968. The system is periodically revised with advance in diagnosis and treatment. (4)

This common language recognizes six main objectives:

- To aid clinicians in treatment planning
- To give some indications on prognosis
- To assist in the evaluation and comparison of treatment results
- To facilitate the exchange of information between different treatment centers.
- To contribute to the continuing investigation of malignant tumors
- To support cancer control activities

Staging and grading

Cancer staging refers to the anatomic extent of the disease spread. The internationally accepted criteria for cancer staging, the tumor-node-metastasis (TNM) system, include:

(a) Tumor size and local growth (T)
(b) Extent of lymph node metastasis (N)
(c) Occurrence of distant metastasis (M).

Typical Descriptions of the Different Stages and Grades

Stage I: Tumor limited to organ of origin, without nodular or vascular spread.

Stage II: Local spread of tumor into surrounding tissue and regional lymph nodes. The lesion is resectable, but there is uncertainty about completeness of removal due to tumor microinvasion of surrounding tissue.

Stage III: Extensive primary tumor with invasion into deeper structures, bone, and lymph nodes. The lesion is operable but not resectable, and gross disease is left behind.

Stage IV: Evidence of distant metastasis beyond tumor organ of origin; primary tumor is inoperable.(6)

STAGE	GROUPING	DESCRIPTIONS
0	Tis, N0, M0	Tis: Ductal or lobular carcinoma in situ N0: No regional lymph node metastasis M0: No distant metastasis
I	T1, N0, M0	T1: Tumor 2cm or less in greater dimension
2A	T0, N1, M0 T1, N1, M0 T2, N0, M0	T2: Tumor more than 2 cm but not more than 5cm in greatest dimension N1: Metastasis to movable ipsilateral axillary lymph node
2B	T2, N1, M0 T3, N0, M0	T3: Tumor more than 5cm in greatest dimension
3A	T0, N2, M0 T1, N2, M0 T2, N2, M0 T3, N1, M0 T3, N2, M0	N2: Metastasis to ipsilateral axillary lymph nodes fixed or matted; or in clinically apparent ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis
3B	T4, N0, M0 T4, N1, M0 T4, N2, M0	T4: Tumor of any size with direct extension to chest wall or skin

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II. METHODOLOGY

Study site:
The study was conducted in the oncology department of Bangalore Baptist Hospital in India.

Study design:
Prospective observational study

Study population:
All patients diagnosed with breast cancer who are undergoing chemotherapy.

Study period:
The study was conducted over a period of 6 months.

Inclusion Criteria:
- Participants are included irrespective of their gender
- Should have complete medical record
- Patients above 18 years of age are included in this study
- Patients undergoing chemotherapy

Exclusive Criteria:
- Pregnant and lactating women
- Incomplete medical record
- Patient seen on urgent basis because a comprehensive medical assessment is not performed during such consultation
- Receiving maintenance dialysis
- Undergoing radiation therapy

Source of data:
- Medication charts.
- Medication history charts.
- Admission and discharge record book.
- Lab data.
- ECG chart.
- Physician/nurse interviews.

Micromedex, Medscape and references books

III. RESULT

The study had a sample size of 60 patients (n=60) of whom all 60 were female patients.

Age distribution

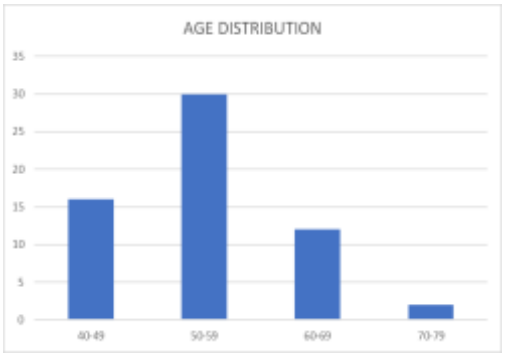

FIG 01: Bar graph showing the age distribution of patients in the study population

STAGING OF BREAST CANCER

STAGE	NO. OF PATIENTS	PERCENTAGE
SECOND	11	18%
THIRD	32	53%
FOURTH	17	28%

Table no.01 shows breast cancer staging in which the third stage is the highest followed by fourth and second stage

ANTICANCER DRUGS

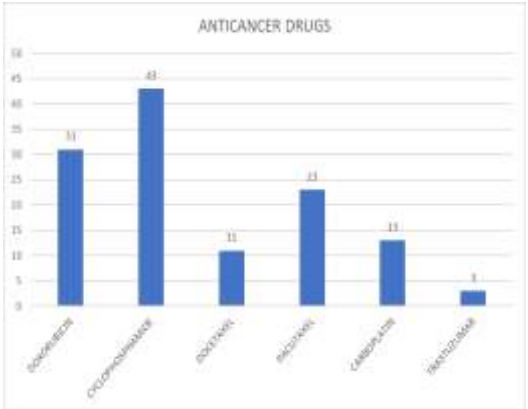

FIG no.2 shows the number of times each drug is used in the treatment of breast cancer in the study population.

Among these anticancer drugs, Cyclophosphamide is used by 43 patients accounting to 72%, and hence is a dominating choice of drug. Doxorubicin on the other hand is used by 31 patients implying 52% of usage. Followed by Paclitaxel used by 23 patients (38%),

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Carboplatin used by 13 patients (22%), Docetaxel used by 11 patients (18%) and the least usage of drug being of Transtuzumab which is used by 3 patients (5%).

TOXICITY

Hematological toxicity

Fig no.3 shows the representation of hematological toxicity observed in patients undergoing chemotherapy shows high risk chances of Anemia with 36 number of patients, yielding to 60% which is the maximum among all the other toxicities, followed by Neutropenia with 35 number of patients (58%), followed by Leukopenia with 22 number of patients (37%), and the least among them being Myelosuppression with 19 patients (32%).

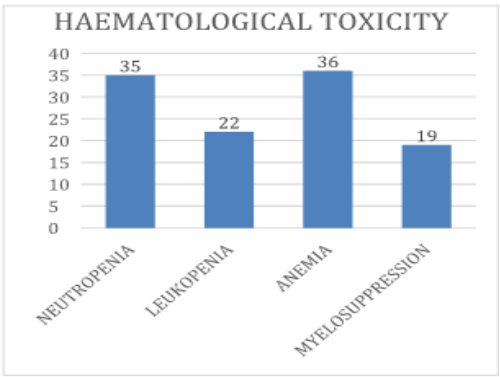

Fig no.3 shows the representation of hematological toxicity

Non-hematological toxicity

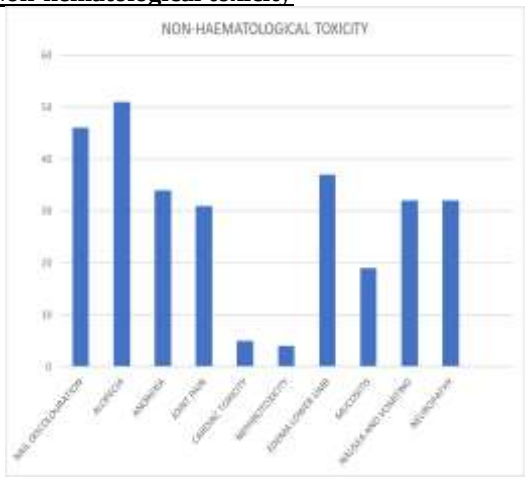

Fig no.4.Bar graph represents non-hematological toxicity observed in patients undergoing chemotherapy for treatment of breast cancer

Fig no.4 shows the representation of non-hematological toxicity observed in patients undergoing chemotherapy shows alopecia with 51 number of patients, yielding to 85%% which is the maximum among all the other toxicities, followed by Nail discoloration with 46 number of patients (77%), followed by edema lower limb with 37 number of patients(62%), followed by anorexia 34 number of patients (57%), followed by nausea and vomiting and neuropathy with 32 number of patients (53%), followed by joint pain with 31 number of patients (52%), followed by mucositis with 19 number of patients (32%), followed by cardiac toxicity with 5 number of patients(8%) and nephrotoxicity with 4 number of patients(7%).

DRUG INTERACTION

In the study, out of 60 patients, 41 patients were found to have suffered from effects of drug interaction. In order to prevent any further complications, the commonly occurring drug interactions were monitored closely and time spacing was advised and followed to the minute because these drug combinations were inevitable for treatment of the patient conditions.

INTERACTING DRUGS	EFFECTS OF INTERACTION
DOXORUBICIN+CYCLOPHOSPHAMIDE	LEADS TO INCREASE RISK OF HEMORRHAGIC CYSTITIS
CARBOPLATIN+DOCETAXEL	LEADS TO INCREASE RISK OF PERIPHERAL NEUROPATHY
CYCLOPHOSPHAMIDE+CARBOPLATIN	MAY RESULT IN ADDITIVE TOXICITIES PARTICULARLY IN THE BONE MARROW AND GASTROINTESTINAL TRACT
CARBOPLATIN+PACLITAXEL	LEADS TO INCREASE RISK OF PERIPHERAL NEUROPATHY

Table no.5. showing the various common drug interactions with their associated effects

ADVERSE DRUG REACTION

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DRUGS	EFFECT	ACTION TAKEN
AC REGIMEN (DOXORUBICIN + CYCLOPHOSPHAMIDE)	LEUKOPENIA JOINT PAIN	PEGFILGRASTIM(IV) DEXAMETHASONE
TAXANES	GASTROINTESTINAL TOXICITY (Nausea and vomiting) (Mucositis) (Anorexia)	PALONOSETRON(IV) PANTOPRAZOLE(IV)
PC (PACLITAXEL + CARBOPLATIN)	ITCHING SKIN RASHES	PHENIRAMINE MALEATE 1 AMP (IV)

IV. CONCLUSION

The age group that was found to be more affected was between 50-59 years of age and the least affected age group was 70-79 years. Left breast was more prone to breast cancer than the right breast. Women with ER-/PR+ and ER-/PR- tumors were somewhat less likely to have lobular, ductal/lobular, mucinous, or tubular carcinomas and were somewhat more likely to have inflammatory, comedo, or medullary carcinomas. Tumors that are HER2 positive tends to be more aggressive, have lower survival rates, and do not often respond to hormonal therapy. The internationally accepted criteria for cancer staging, the tumor-node-metastasis (TNM) system. Clinical stage is established before initiation of therapy and depends on the physical examination, laboratory finding and imaging studies. Pathologic stage is determined following surgical exploration of disease spread. In the treatment of Breast cancer, Cyclophosphamide, Doxorubicin, Paclitaxel, Carboplatin, Docetaxel and Transtuzumab was used. Among these AC regimens (Anthracycline and Cyclophosphamide) was the most commonly used.

The toxicity of chemotherapy is divided into hematological and non-hematological toxicity.Hematological toxicity includes anemia, neutropenia, leukopenia and myelosuppression. Non-hematological toxicity includes nail discoloration, anorexia, nausea and vomiting, neuropathy, joint pain, mucositis, cardiac toxicity and nephrotoxicity.

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