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A STUDY ON EFFICACY OF PRE-MEDICATIONS IN THE MANAGEMENT OF HYPERSENSITIVITY REACTIONS ASSOCIATED WITH CHEMOTHERAPY AMONG BREAST CANCER PATIENTS

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ABSTRACT: -

Background: The estimation of 2.3 million (11.7% of all cancer cases) new cases of breast cancer diagnosed every year globally, the death rate increased over the last 3 decades, it is the 5th leading cause of mortality worldwide with 685000 deaths. Chemotherapy is a crucial component of breast cancer treatment, yet it is often accompanied by the risk of hypersensitivity reactions (HSRs).

Objective: Evaluating hypersensitivity reactions in breast cancer patients involves assessing the effectiveness of premedication, treatment methods, and standardized desensitization protocols to manage reactions and implementing risk management measures.

Methodology: This is Hospital based prospective observational study was conducted in ESI hospital Indira nagar Bangalore, the present study was conducted among 85 patients for a period of six months from April 2023 – September 2023, involves breast cancer patients receiving chemotherapy.

Results: Among the 85 breast cancer patients in our study, 40% were in stage 2 were classified as having a major disease severity, while only 5.88% of those in stage 4 had the lowest severity. Hypersensitivity reactions were prevalent, with 64.7% experiencing grade I and II reactions, and 35.29% having grade III and IV reactions. Notably, platinum agents, specifically carboplatin and oxaliplatin, were responsible for hypersensitivity reactions in 54.11% of cases, while taxanes (paclitaxel and docetaxel) were associated with reactions in 32.9% of cases. Additionally, 38% of the participants received monoclonal antibodies as part of their treatment.

Conclusion: Breast cancer patients receiving chemotherapy, the present study found significant presence of hypersensitivity reactions, with the majority falling into grade I and II categories. These reactions were most commonly associated with platinum agents and taxanes. A substantial portion of patients received monoclonal antibodies as part of their treatment. These findings underscore the need for tailored premedication protocols and risk management measures to improve the safety and efficacy of breast cancer therapy, particularly for those at risk of hypersensitivity reactions. **Key words:** Breast cancer, Hypersensitivity reactions, Premedication, Desensitization.

INTRODUCTION: Breast cancer is the most common cancer in women, with the highest incidence and a leading cause of cancer-related deaths worldwide, typically occurring after puberty and mainly after the age of 40 years. Although rare, men can also develop breast cancer. The World Health Organization (WHO) defines breast cancer as the abnormal growth of breast cells, forming tumors that can be either non-cancerous (benign) or cancerous (malignant). Breast cancer is a diverse disease with various biological and molecular characteristics, including hormone receptor activation, BRCA gene mutations, and HER2 activation. Understanding this heterogeneity is crucial for effective therapeutic intervention and prevention.

Types of breast cancer Non-invasive (in situ) breast cancer, Invasive (infiltrating) breast cancer, Invasive ductal carcinoma (IDC), Invasive lobular carcinoma (ILC), Metastatic breast cancers. Breast cancer is typically staged to describe the extent and severity of the disease and helps in determining the prognosis and treatment options. The commonly used staging system for breast cancer is the TNM (Tumor, Nodes and Metastasis). The primary signs and symptoms of breast cancer include the detection of a lump in the breast, which accounts for over 80% of cases found through self-discovery, Mammograms can detect breast cancer in its early stages, lumps in the armpit lymph nodes, thickening of breast tissue, changes in breast size or position, alterations in nipple appearance, skin changes like dimpling or puckering, nipple discharge, persistent breast or armpit pain, and swelling around the collarbone or under the armpit.

Risk factors: Breast cancer risk factors can be categorized into modifiable and non-modifiable factors. Modifiable risk factors include hormone replacement therapy, physical inactivity, obesity, alcohol consumption, smoking, and dietary choices. Non-modifiable risk factors include female gender, older age, genetic mutations, and family history of breast cancer, race/ethnicity, and reproductive factors like pregnancy history. Understanding these risk factors is crucial for breast cancer prevention and early detection. It's important to consider both types of risk factors to make informed decisions about lifestyle changes and screening.

Screening and diagnosis: Mammography, Clinical Breast Exam (CBE), Breast Self-Exam, Magnetic Resonance Imaging (MRI), Genetic Testing, Risk Assessment Tailored screening based on individual risk factors. Diagnosing breast cancer involves a triple test approach clinical examination, imaging (mammography and/or ultrasonography), and needle biopsy. This assessment helps distinguish between breast cancer, benign conditions, and cases where surgical intervention is not needed. Ultrasonography is often used in young women and for characterizing abnormalities detected during screening. MRI is reserved for specific clinical situations, especially in cases with inconclusive results or invasive lobular cancers.

Treatment modalities included Surgery, Radiation therapy, Hormonal therapy, Targeted therapy, Chemotherapy

Chemotherapy: Chemotherapy is a systemic treatment for breast cancer. The choice of neoadjuvant or adjuvant chemotherapy depends on the tumor's characteristics. It's also used in cases of secondary breast cancer. Various drug combinations are used intravenously or orally, targeting specific molecular subtypes. Common drugs used in breast cancer - Taxanes: paclitaxel, docetaxel, Platinum Complexes: carboplatin, oxaliplatin, cisplatin, Antimetabolites: Methotrexate, 5-fluorouracil, capecitabine, epirubicin, eribulin, Alkylating Agents: Cyclophosphamide, ifosfamide, Targeted Drugs (Monoclonal Antibodies): trastuzumab, pertuzumab, Miscellaneous: Doxorubicin, NAB-Paclitaxel, Combination Therapies: Various combinations of the above drugs, Targeted Therapy + Chemotherapy: Combinations of chemotherapy drugs with targeted therapies like trastuzumab and pertuzumab. Common regimens include AC-T (doxorubicin and cyclophosphamide followed by paclitaxel), dose-dense AC-T (administered every 2 weeks), and DAC (docetaxel with AC). Weekly paclitaxel or every 3-weekly docetaxel are alternative schedules. These regimens have varying levels of effectiveness and toxicity. Chemotherapy plays a critical role in treating breast cancer, but its specific use and regimen are determined based on individual patient and tumor characteristics. It can be a potent tool against cancer, but it may also result in various side effects.

Hypersensitivity: Hypersensitivity reactions characterized by an exaggerated or inappropriate immune response leading to adverse effects on the body. These reactions are associated with antigen-antibody interactions and are categorized into four types: type I, II, III, and IV. Depending on the rapidity and nature of the immune response, these hypersensitivity reactions can be grouped into immediate and delayed types. Immediate hypersensitivity reactions occur rapidly, involving humoral antibodies and mediated by B cells, and include types I, II, and III. On the other hand, delayed hypersensitivity reactions have a slower onset, typically within 24-48 hours, are prolonged in their effects, and are primarily mediated by cellular responses, particularly T cells, represented by Type IV reactions.

Diagnostic Tests for Hypersensitivity Reactions: Skin Prick Test, Blood Tests, Patch Test , Radio Allegro Sorbent Test (RAST), Basophil Activation Test (BAT), Serum Tryptase, Lymphocyte Transformation Test (LTT), Allergy Challenge Tests.

Signs and symptoms: Allergic reaction/hypersensitivity (including drug fever), Pruritus/itching, Rash/desquamation, Urticaria (hives, welts, wheals), Rigors/chills, Headache, Arthralgia/myalgia, Tumor pain, Fatigue (asthenia, lethargy, malaise), Dizziness, Sweating, Nausea/vomiting, Cough, Dyspnea, Bronchospasm, Hypotension/hypertension , Tachycardia.

PREMEDICATIONS: Premedications are commonly used to manage hypersensitivity reactions during chemotherapy, especially when drugs known to cause allergic reactions are prescribed. Common premedications include antihistamines, corticosteroids, and leukotriene receptor antagonists, which can reduce the risk and severity of hypersensitivity reactions. Some examples for premedication are: Corticosteroids, Methylprednisolone, Ondansetron, Diphenhydramine, Ranitidine, Montelukast, Dopamine , Atropine and Vasopressin.

1. In cases of suspected anaphylaxis, administer Epinephrine 0.2-0.5 mg (1 mg/mL) intramuscularly, repeating every 5-15 minutes. Additionally, use H1/H2 antagonists with diphenhydramine 50 mg intravenously and ranitidine 50 mg intravenously. If bradycardia is present, consider atropine 600 µg intravenously. For patients on beta-blockers, administer glucagon 1-5 mg intravenously over 5 minutes. Administer corticosteroids at a dose equivalent to 1-2 mg/kg of intravenous (methyl) prednisolone every 6 hours. In cases of hypotension, use either Dopamine at 2-20 µg/kg/min in

400 mg diluted in 500 mL or Vasopressin at a dose of 0.01–0.04 U/min in 25 U diluted in 250 mL of 5% dextrose in water or normal saline (0.1 U/mL). Additionally, provide normal saline as a 1-2 L intravenous infusion at a rate of 5-10 mL/kg in the first 5 minutes, followed by crystalloids or colloids in boluses of 20 mL/kg, followed by slow infusion.

2. For suspected cytokine-release/HSR, adjust the infusion rate based on severity: Grade 1 with a slow infusion, Grade 2 with a slow rate or short-term cessation, and Grade 3/4 by stopping the infusion. Treat with H1/H2 antagonists (diphenhydramine 50 mg intravenously and ranitidine 50 mg intravenously) and corticosteroids at a dose equivalent to 1-2 mg/kg of intravenous (methyl) prednisolone every 6 hours. Restart the infusion at 50% rate and titrate to tolerance. Re-administer H1/H2 antagonists and corticosteroids, but re-challenge is discouraged in severe reactions.

DESENSITIZATION: Drug desensitization is a medical procedure designed to build patient tolerance to medications causing hypersensitivity reactions. Originally for antibiotic allergies, it's now used in chemotherapy and biologic treatments. The procedure, known as Rapid Drug Desensitization (RDD), addresses a range of drug allergies, from skin rashes to life-threatening anaphylaxis. RDD allows continued use of preferred treatments, employing protocols to establish temporary drug tolerance. It's safe, effective, and applicable across various reactions, including in patients of any age, even pregnant individuals. By preventing severe hypersensitivity reactions, RDD ensures uninterrupted essential medication for critically ill patients.

AIM AND OBJECTIVES:

Aim: To evaluate and manage of hypersensitivity reactions associated with chemotherapy among breast cancer patients.

Objectives:

- Evaluating hypersensitivity reactions in breast cancer patients
- Efficacy of premedication to hypersensitivity reactions management among breast cancer patients.
- The effective methods used to prevent and treat hypersensitivity reactions in breast cancer patients.
- Standardized rapid desensitization protocol for achieving temporary tolerization to drug allergens.

METHODOLOGY: This study is a prospective, observational, study was carried out for the critical analysis and evidence based study.
This study focused on efficacy of premedication in the management of hypersensitivity reactions associated with chemotherapy among breast cancer patients-risk factor predictions in prevention of hypersensitivity reactions.

Study design: It is a hospital based prospective, observational study.
Study site: Study was conducted in ESI Indiranagar Bangalore, Karnataka, India.
Sample size: The estimated sample size was among 85 patients in the department ESI Indiranagar
Study period: The present study conducted for a period of six months from April 2023 – September 2023

Study criteria:
Inclusion Criteria:

- Patient's cases are collected April 2023 to September 2023.
- Patients who are willing to participate in the study.
- Patients who are receiving premedications before chemotherapy.
- Chemotherapeutic agents include the class of monoclonal antibodies, platinum agents, taxanes.

Exclusion Criteria:

- Patients who are unwilling to participate in the study.
- Chemotherapeutic Patients except receiving Monoclonal antibodies, Taxanes, and Platinum agents.

Source of data:

- Data is collected through patient interview, physical examination of patients at ESI hospital.
- The details collected in data collection form includes patient's demographics, hypersensitivity reactions, progressive chart details, patient past and present medication history.
- The proposed study was approved by Institutional ethics committee (IEC).

Tools used:

RESULTS: The sample of the present study is 85 individuals**,** Data collection includes patient demographics, chemotherapy regimens, premedication protocols, occurrence of HSRs, and their outcomes.

PARAMETERS (AGE IN YEARS)	GENDER	
	FEMALE	
	NUMBER	PERCENTAGE (%)
20-30	4	4.70%
30-40	11	12.94%
40-50	17	20.0%
50-60	20	23.5%
60-70	22	25.88%
70-80	10	11.76%
80-90	2	2.35%

Table 1: Demographic details of the subjects

Among the study, the table 1 categorizes a group of 85 individuals into different age groups condition patients. The largest portion, 25.88%, falls within the 60-70 age range, closely followed by 23.52% in the 50-60 age range, 20% of patients are within 40-50 age, 12.94% is 30-40 and 70-80 age group patients. A smaller proportion, 4.70% is aged 20-30 while another 2.35% are80-90 years old.

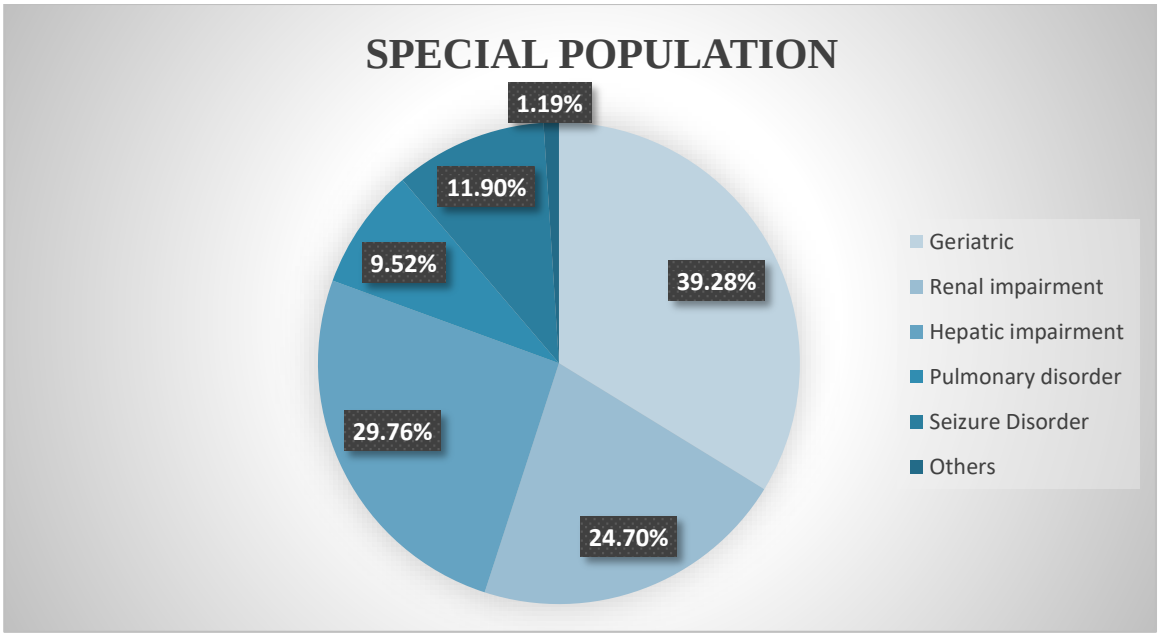

Figure 1: Pie chart showing special patients.

Pie chart representing among 85 patients 33 (39.28%) are the geriatric patients 25 (29.52%) patients are hepatic impairment, 21 (24.70%) patients are renal impairment, 10 (11.90%) patients are having seizure disorder, 8 (9.52%) patients are having pulmonary disorder, remaining 1.19% of people having other disorders.

DURATION OF BREAST CANCER	NUMBER	PERCENTAGE
01-03years	54	63.52%
03-06years	19	22.35%
06-09years	12	14.11%
Total	85	100%

Table 2: Distribution of study subject based on duration of breast cancer.

Among the study, the table 2 categorizes a group of 85 individuals facing breast cancer around 3 years of duration 54 patients (63.52%) were suffering, around 5 years of duration 19 patients (22.35%) were suffering and around 9 years 12 patients (14.11%) were suffering from the breast cancer.

STAGE OF BREAST CANCER	NUMBER OF PATIENTS	PERCENTAGE
STAGE 1	10	11.76%
STAGE 2A	19	22.35%
SATGE 2B	15	17.64%
STAGE 3A	10	11.76%
STAGE 3B	12	14.11%
STAGE 3C	07	8.23%
STAGE 4	05	5.88%

Table 3: Distribution of number of patients and percentage hypersensitivity patients based on stage of breast cancer

The table reflects that, the distribution of number of patients and percentage based on stage of breast cancer is, stage 1 are 10 patients (11.76%), stage 2A are 19 patients (22.35%), stage 2B are 15 patients (17.64%), stage 3A are 10 patients (11.76%), stage 3B are 12 patients (14.11%), stage 3c are 07 patients (8.23%), and stage 4 are 5 patients (5.88%).

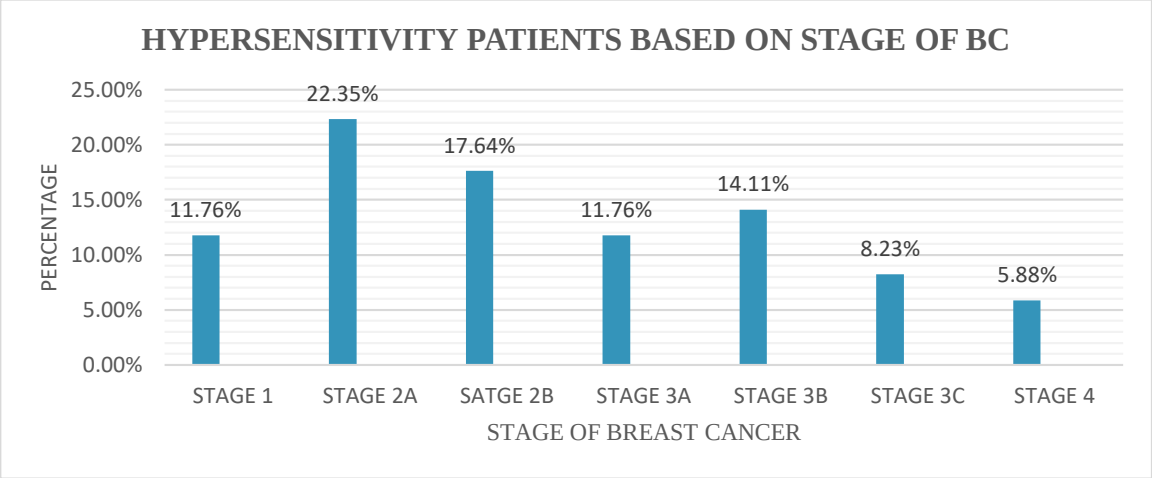

Figure 2: Distribution of number of patients and percentage hypersensitivity patients based on stage of BC

The figure 2 distribution of number of patients and percentage based on stage of breast cancer is, stage 1 are 10 patients (11.76%), stage 2A are 19 patients (22.35%), stage 2B are 15 patients (17.64%), stage 3A are 10 patients (11.76%), stage 3B are 12 patients (14.11%), stage 3c are 07 patients (8.23%), and stage 4 are 5 patients (5.88%).

S.NO	DRUGS	NUMBER OF PATIENTS USED	PERCENTAGE
1.	Monoclonal antibodies		
	Trastuzumab	26	30.58%
	Pertuzumab	7	8.23%
2.	Platinum agents		
	Carboplatin	30	35.29%
	Oxaliplatin	16	18.82%
3.	Taxanes		
	Paclitaxel	9	10.58%
	Docetaxel	19	22.35%
4.	Miscellaneous		
	Doceaqualip	8	9.41%
	Nab-paclitaxel	7	8.23%

Table 4: Distribution of patient number and percentage based on drugs used in BC chemotherapy

This table 4 provides an overview of medication usage among 85 individuals. 38.81% of patients were receiving monoclonal antibodies the drugs are Trastuzumab 30.58%, 8.23% patients are receiving Pertuzumab. 54.11% were the platinum co-ordination agents are the

main drugs are carboplatin 35.29% and oxaliplatin is 18.82%. The main class of drugs used is taxanes 32.93% the drugs are paclitaxel 10.58% and docetaxel 22.35%. Another miscellaneous drugs are doceaqualip 9.41% and NAB-paclitaxel is 8.23%.

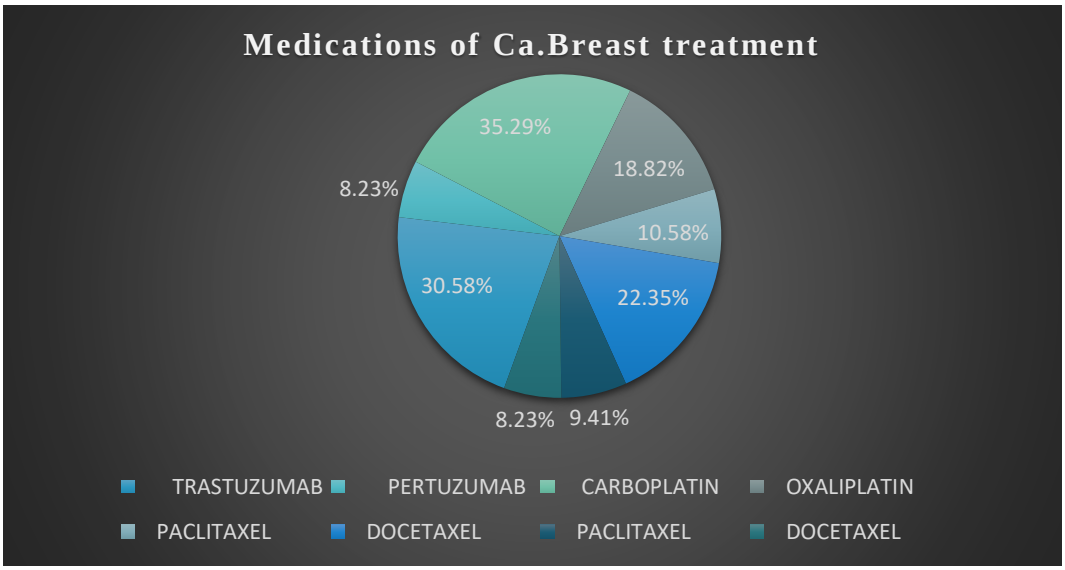

Figure: 3 Distribution based on drugs used in BC chemotherapy.

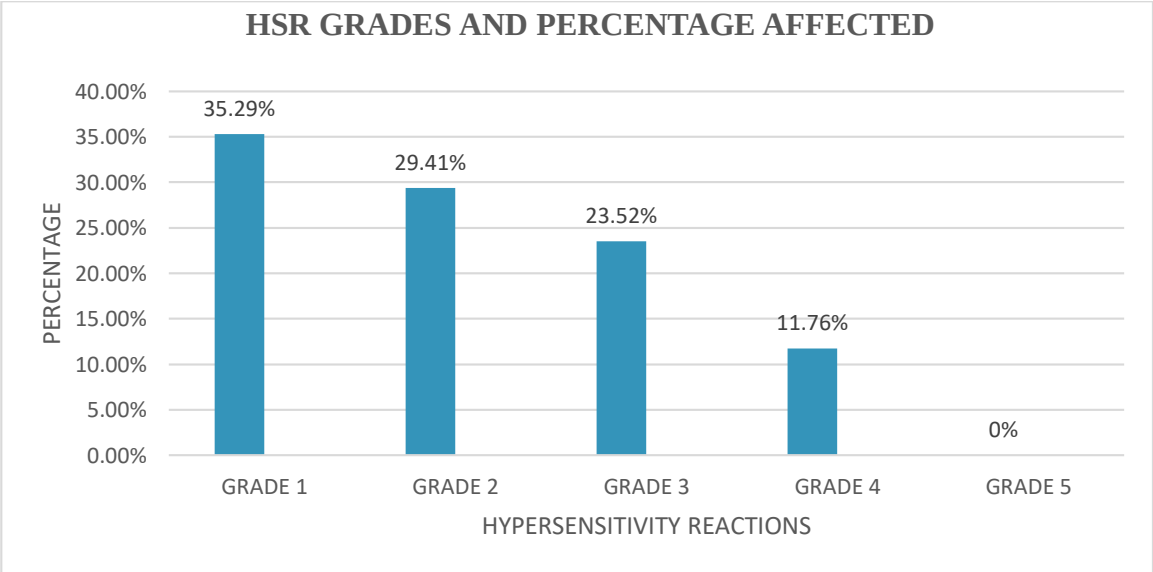

Figure 4: Hypersensitivity reactions Grades

This figure 4 provides the information about study of 85 individual having hypersensitivity reactions of grade 1 were 30(35.29%) people, grade 2 are 25 (29.41%) people, grade 3 are 20(23.52%) people and grade 4 were 10(11.76%) people

TREATMENT	TAXANES	PLATINUM AGENTS	MONOCLONAL ANTIBODIES	OTHERS
Number of patients	28	46	33	15
Percentage	32.9%	54.11%	38.82%	17.64%

Table 5: Number of patients received treatment for hypersensitivity reactions to taxanes, platinum agents and monoclonal antibodies

Among 85 people the distributd number of patients who received treatment for hypersensitivity reactions occurred due to taxanes are 28 patients (32.9%), patinum agents 46 patients (54.11%), monoclonal antibodies 33 patients (38.82%) and other drugs are 15 patients(17.64%).

Table 6 : Premedication drugs used in the study subject.

PREMEDICATION	NUMBER	PERCENTAGE
Corticosteroids	13	15.29%
Antiemetic's	13	15.29%
Antihistamine	13	15.29%
Histamine 2 antagonist	13	15.29%
Proton pump inhibitor	5	5.88%
Leukotriene antagonist	9	10.58%
Catecholamine	6	7.05%
Anticholinergic	5	5.88%
Antidiuretic	8	9.41%
Total	85	100%

Table 6 indicates that 85 patients involved in the study are received oral premedication's as per their treatment protocol, in that 15.29% of the patients received corticosteroids, 15.29% of the Patients received antiemetic drugs, 15.29% of patients received antihistamines, 15.29% of patients received histamine 2 antagonist, 10.58% of patients are received leukotriene antagonist, 9.41% of patients received antidiuretics, 7.05% of patients received catecholamines, and 5.88% of patients received proton pump inhibitor and 5.88% of patients received anticholinergic. .

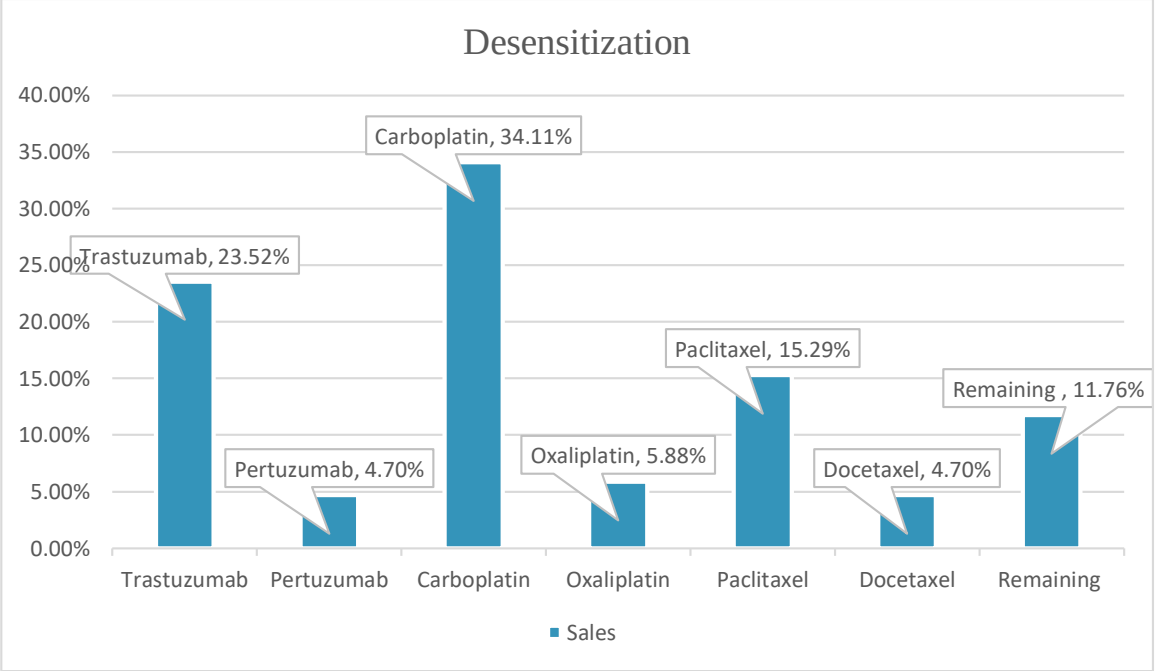

Figure: 5 Distribution of Desensitization procedure incurred in the patients with chemotherapy treatment among breast cancer.

Out of 85 people in the study 20 individuals (23.52%) are received transtuzumab desensitization procedure, 4 individuals (4.70%) are pertuzumab, 29 individuals (34.11%) are carboplatin, 5 individuals (5.88%) are oxaliplatin, 13 individual (15.29%) are paclitaxel, 4 individuals (4.70%) are docetaxel and 10 individuals (11.76%) are not undergone any desensitization till.

DISCUSSION:

A study conducted by Rahel aberaraw et.al and Sandra M swain et.al. the studies are reported results are similar to my study. Among the study, the table categorizes a group of 85 individuals into different age groups condition patients. The largest portion, 25.88%, falls within the 60-70 years age range, closely followed by 23.52% in the 50-60 age range, 20% of patients are within 40-50 age, 12.94% is 30-40 and 70-80 age group patients. A smaller proportion 4.70% is aged 20-30 while another 2.35% are 80-90 years old.

A similar demographics has reported by Sandra M swain et.al. Similarly, the 39.28% were geriatric patients, 24.70% were renal impairment patients and 29.76% hepatic impairment patients. Out of 85 patient's co-morbid condition distributed as 29.76% diabetes mellitus, 24.70% are CKD patients, 9.52% are pulmonary disorder and 11.90% were seizure disorder

Fadi M. Alkabban conducted study is having similar information to my study the results. Among the study, the table categorizes a group of 85 individuals facing breast cancer around 3 years of duration 54 patients (63.52%) were suffering, around 5 years of duration 19 patients (22.35%) were suffering and around 9 years 12 patients (14.11%) were suffering from the breast cancer.

Similarly was seen with the results of the study conducted by Ming li et.al and sepideh saadatmand et.al. The distribution of number of patients and percentage based on stage of breast cancer is, stage 1 are 10 patients (11.76%), stage 2A are 19 patients (22.35%), stage 2B are 15 patients (17.64%), stage 3A are 10 patients (11.76%), stage 3B are 12 patients (14.11%), stage 3c are 07 patients (8.23%), and stage 4 are 5 patients (5.88%).

The researcher Tracy-ann Moo et.al, publishes the overview of breast cancer treatment and similarly by referring world health organization guidelines for breast cancer therapy and JNCNN guidelines of 2023 are taken for the reference for my study. An overview of medication usage among 85 individuals, 38.81% of patients were receiving monoclonal antibodies the drugs are Trastuzumab 30.58%, 8.23% patients are receiving Pertuzumab. 54.11% were the platinum co-ordination agents are the main drugs are carboplatin 35.29% and oxaliplatin is 18.82%. The main class of drugs used is taxanes 32.93% the drugs are paclitaxel 10.58% and docetaxel 22.35%. Another miscellaneous drugs are doceaqualip 9.41% and NAB-paclitaxel is 8.23%.

The Researcher J.Boulanger et.al study is similar to my study results, This table provides the information about study of 85 individual having hypersensitivity reactions of grade 1 were 30(35.29%) people, grade 2 are 25 (29.41%) people, grade 3 are 20(23.52%) people and grade 4 were 10(11.76%) people.

The 85 patients involved in the study are received oral premedication's as per their treatment protocol, in that 15.29% of the patients received corticosteroids, 15.29% of the Patients received antiemetic drugs, 15.29% of patients received antihistamines, 15.29% of patients received histamine 2 antagonist, 10.58% of patients are received leukotriene antagonist, 9.41% of patients received antidiuretics, 7.05% of patients received catecholamines, and 5.88% of patients received proton pump inhibitor and 5.88% of patients received anticholinergic. Jull M.Cox et.al. study results are similar to the present study result.

The results of K.Scherer et.al. research are similar to this study that is, Out of 85 people in the study 20 individuals (23.52%) are received transtuzumab desensitization procedure, 4 individuals (4.70%) are pertuzumab, 29 individuals (34.11%) are carboplatin, 5 individuals (5.88%) are oxaliplatin, 13 individual (15.29%) are paclitaxel, 4 individuals (4.70%) are docetaxel and 10 individuals (11.76%) are not undergone any desensitization till.

CONCLUSION: This study concluded that breast cancer patients receiving chemotherapy, found a significant presence of hypersensitivity reactions, with the majority falling into grade I and II categories. These reactions were most commonly associated with platinum agents (carboplatin and oxaliplatin) and taxanes (paclitaxel and docetaxel). A substantial portion of patients received monoclonal antibodies as part of their treatment. These findings underscore the need for tailored premedication protocols and risk management measures to improve the safety and efficacy of breast cancer therapy, particularly for those at risk of hypersensitivity reactions.

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CONFLICT OF INTEREST -None declared.
ETHICAL APPROVAL- The study was approved by Institutional Ethics Committee.

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