Prescribing Pattern of Chemotherapy Regimens In Breast Cancer

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ABSTRACT

Cancer is a disease of abnormal, uncoordinated, uncontrolled and purposeless cell division in any part of body. The leading cause of death in women is due to breast cancer that accounts for 12.7% around the globe. This study aims to describe the prescribing trends and possible avenues for improving of chemotherapy drugs in breast cancer patients. The prospective observational was conducted among 178 patients in the Medical Oncological Department of Apollo Multispecialty Hospital and Research Center for a period of 6 months. The data was assessed and evaluated using statistical tool. The number of patients receiving adjuvant, neoadjuvant and palliative therapy was 131,10 and 37 respectively. The most commonly prescribed drug as monotherapy in adjuvant, neoadjuvant and palliative therapy was paclitaxel (14.5%) or zoledronic acid (14.5%), trastuzumab (40%) and zoledronate (45.9%) respectively. The most commonly prescribed combinational regimens drug in adjuvant, neoadjuvant and palliative therapy was Cyclophosphamide with Docetaxel (15.30%), Cyclophosphamide with Docetaxel (20%) or cyclophosphamide with Epirubicin (20%) and Letrozole with zoledronate (21.6%). Dexamethasone, ondansetron and pantoprazole (100%) were co administered in all the patients during their chemotherapy cycles. The observed side effects were back pain, anemia, neutropenia, insomnia, anxiety, myalgia, cough. The prescribed chemotherapy drugs for the breast cancer meet the criteria of patient’s adherence. Breast cancer is a prevalent type of cancer that require long term therapy and monitoring to evaluate and refine the therapeutic regimen of breast cancer to provide the extension and better quality of life.

Keywords: Cancer, Breast cancer, Chemotherapy, prescribing trends

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INTRODUCTION

Cancer is a disease of abnormal, uncoordinated, uncontrolled and purposeless cell division in any part of the body.[1] Apoptosis or programmed cell death in normal tissues is replaced by uncontrolled cell growth in cancer cells.[2] Breast cancer initiates when cells in the breast begin to grow uncontrollably. The breast cancer includes several risk factors such as early menarche, late menopause, genetic and epigenetic reasons, family history of breast cancer, race and ethnicity, having dense breast tissue, drinking alcohol, and being overweight. [3] Breast cancer is the most common cancer (about 25% of all cancers) among women in 2012 where 1.67 million new cases were diagnosed and about 70,218 women died of this cancer (mortality of 21.5% of all cancer cases). Therefore, the leading cause of death in women with cancer is breast cancer with a mortality rate of 12.7 per lakh population.[4]

The main modalities used for breast cancer treatment include chemotherapy, hormonal therapy, immunotherapy, radiation therapy, surgery. The choice of therapy depends on patient factors, tumor factors, and treatment factors. There are different types of chemotherapy that include adjuvant chemotherapy, neoadjuvant chemotherapy, and palliative chemotherapy. In olden days, cancers were treated with a single drug; but, nowadays, the combination of drugs is given to overcome the cancer cell heterogeneity and development of drug-resistant cells to kill total tumor cells.[5]

Several drugs such as 5-fluorouracil, epirubicin, doxorubicin, cyclophosphamide, docetaxel/paclitaxel, trastuzumab, tamoxifen, Palbociclib, Fulvestrant, letrozole, and carboplatin are prescribed to tackle such type of patients.[3] Chemotherapy regimens are highly complex and associated with intolerable adverse effects. In a study of adverse drug reactions due to chemotherapeutic agents in Oncology patient’s highest incidence of an adverse drug reactions were reported in patients treated for breast carcinoma (39.1%).[6]

Evaluation of prescribing patterns of anticancer drugs is essential due to the availability of different regimens, the variable response rate with different drugs and the intolerability of combination regimens. Drug utilization studies (DUS) provide useful tools to assess the appropriateness of therapy, identify areas that need improvement to make medical care rational, cost-effective and standard quality.[7] By evaluating and comparing the prevailing pattern with existing standards, necessary steps can be taken to optimize anticancer therapy with improved efficacy and minimal toxicity. Cisplatin (19.6%) was found to be the most common offending drug. The most common chemotherapy adverse drug reactions reported were nausea and vomiting (23%) and Gastroenterology (40.1%) was the most affected system. About 50.2% of the adverse drug reactions
required treatment and 12.9% of adverse drug reactions were considered serious. Causality assessment in chemotherapy revealed that 80% of the adverse drug reactions were possible. About 86.97% of cases were found to be mild, and 51% were not preventable.\textsuperscript{[6]}

**MATERIALS AND METHOD**

A prospective observational study was conducted for 6 months from October 2018 to March 2019 in the Department of Medical Oncology at Apollo Multi-Specialty Hospital and Imperial Cancer Research Center (JCI &NABH), Bengaluru. The study was conducted in 178 patients who satisfied the study criteria. The study included patients of all age groups with breast cancer receiving chemotherapy. Pregnancy and lactating women were excluded from the study. All the necessary details for the study were collected from the patient's medical record at the inpatient department, and the medical records were reviewed on a daily basis. The information such as age, gender, past medical history, presence of comorbidities, type of cancer, stage of cancer, and drug therapy was convened systematically and archived in the data collection form. The study was cleared ethically by the Institutional Ethics Committee (IECCS of Apollo hospitals, Bengaluru) with reg. number ECR/320/inst/KA/2013/RR-16. Prescribing patterns of chemotherapy were analysed by collecting the details of drug usage including drug name, dose, indication, dosage form, frequency, duration, route of administration, chemotherapy cycles, and chemotherapy regimens and these were recorded in the data collection form. Similarly, the prescribing pattern of supportive drugs used along with cancer chemotherapy was also recorded from the drug treatment chart and convened in the data collection form. The study was analysed using a chi-square test of independence of attribution using statistical software i.e. SPSS version 23.0.

**RESULTS AND DISCUSSION:**

Alteration in chemotherapy regimen and supportive care medications are based on the variability of patients, demographic details, cancer types, and stages of cancer and depend on the expected toxicities, thus it is necessary to evaluate the prescribing patterns of anticancer and supportive care drugs in breast cancer patients.

A total of 178 patients with breast cancer were enrolled in the study. In this study, most of the patients were in the age group of 51-60 years (32%) followed by 61-70 years (31.5%); this was in correspondence with the study carried out by American Cancer Society published in Breast Cancer Facts and Figures 2017-2018 stated that women age 50-70 years had more rate of developing Breast cancer. The rate of breast cancer was lower after 80 years due to a higher mortality rate.\textsuperscript{[8]} The Immunohistochemistry (IHC) status was classified on the basis of Estrogen Receptor (ER),
Progesterone Receptor (PR), Human Epidermal growth factor Receptor 2 (HER2) and ki67. The highest Immunohistochemistry status group was in luminal B (50.60%) while the lower Immunohistochemistry status group was unclassified (1.70%). Similar finding was found in the study on “Breast cancer intrinsic subtype classification, clinical use and future trends” conducted by Xiofeng Dai, Ting Li, Zhonghu Bai, Yankun Yang, Xiuxia, Jinling Zhan, et al state that Luminal B (52.8%) was the highest subtypes class and unclassified or normal (7.8%) like was the least.[9]

The data of patients with breast cancer were recorded, having comorbidities during cancer registration or comorbidities diagnosed during treatment. 66.9% of patients had no comorbidities and hypertension (11.2%) was the most comorbidities associated with breast cancer. The lowest percentage of comorbidities were found in several groups like as Hepatitis B; DM, hypertension, Thrombosis; Bronchial Asthma; HTN, CAD; HTN, PAH; HTN, PM, Asthma; Pneumonitis; TAH & BSO. Each of these groups represented 01 patient with a percent of 0.6%. Similar finding was found in the study of “association of comorbidities with breast cancer: an observational study” conducted by Neeti Sharma, Satya Narayan, Rajani Sharma, Anil Kapoor, Narendra Kumar and Rajkumar Nirban that was published on Tropical Journal of Medical Research stated that hypertension was the most comorbidities associated with breast cancer with a prevalence of 21.8%.[10]

On the basis of types of chemotherapy received, 178 patients were grouped into three categories which include palliative therapy, adjuvant therapy, and neoadjuvant chemotherapy. The prescribed adjuvant chemotherapy, neoadjuvant chemotherapy, and palliative chemotherapy was observed in 131, 10 and 37 patients respectively. The adjuvant chemotherapy was highest given in 131 patients (73.6%). Neoadjuvant chemotherapy was lowest given in 10 patients (5.6%). A similar finding was found in the study conducted on “Study of Prescription pattern and adverse drug reaction” by Renuka L K, Vijay M, Smita, Diwan A K that 50 patients (71.4%) received adjuvant chemotherapy and neoadjuvant chemotherapy was given to 05 patients (7.1%).[11] The demographic details of the study population are summarized in Table 1. The higher types of breast cancer patients were right breast cancer (53.90%) followed by left breast cancer (44.90%), right and left breast cancer (1.2%). The majority of the breast cancer patients were diagnosed with Stage I (42.68%) followed by Stage IV (29.21%), Stage III (20.79%) and Stage II (7.30%) as described in table 1 and 2.
Table 1: Demographics of the study population

| Demographic details | Number of patients (n=178), (%) |
|---------------------|---------------------------------|
| Age group(year)     |                                 |
| < 30 years          | 06 (03.4%)                      |
| 31-40 years         | 14 (7.9%)                       |
| 41-50 years         | 30 (16.9%)                      |
| 51-60 years         | 57 (32.0%)                      |
| 61-70 years         | 56 (31.5%)                      |
| 71-80 years         | 14 (7.9%)                       |
| >80 years           | 01 (0.6%)                       |

Chi square test= 125.36, p value < 0.05

Breast intrinsic subtype classification (High-status)

| Base like (triple negative) | 33 (18.50%) |
|-----------------------------|-------------|
| Her2 enriched               | 20 (11.20%) |
| Luminal A                   | 32 (18.00%) |
| Luminal B                   | 90 (50.60%) |
| Unclassified                | 03 (01.70%) |

Chi square test= 125.11 & p value < 0.05

Diagnosis

| Left breast cancer | 80 (44.9%) |
|--------------------|------------|
| Right breast cancer| 96 (53.9%) |
| Right + left breast cancer | 02 (1.2%) |

Stage

| Stage I (T_{1-2}N_{0-1}M_{0}) | 76 (42.68%) |
|-------------------------------|-------------|
| Stage II (T_{3-4}N_{0-1}M_{0}) | 13 (7.30%) |
| Stage III (T_{any}N_{2-3}M_{0}) | 37 (20.79%) |
| Stage IV (T_{any}N_{any} M_{1}) | 52 (29.21%) |

Chemotherapy type

| Adjuvant chemotherapy | 131 (73.6%) |
|-----------------------|-------------|
| Neoadjuvant chemotherapy | 10 (5.6%) |
| Palliative chemotherapy | 37 (20.8%) |

Table 2: Categories of patients according to stage T, N & M.

| Stage T | Stage N | Stage M | Total |
|---------|---------|---------|-------|
| 1       | 0       | 20      | 20    |
| 1       | 8       | 0       | 8     |
| 2       | 7       | 2       | 9     |
| 3       | 2       | 1       | 3     |
| **Total** | **37** | **3** | **40** |
| 2       | 0       | 28      | 30    |
| 1       | 20      | 7       | 27    |
| 2       | 7       | 4       | 11    |
| 3       | 7       | 0       | 7     |
| **Total** | **62** | **13** | **75** |
| 3       | 0       | 2       | 3     |
| 1       | 6       | 2       | 8     |
| 2       | 3       | 12      | 15    |
| 3       | 5       | 0       | 5     |
| **Total** | **16** | **15** | **31** |
| 4       | 0       | 1       | 1     |

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Patients receiving adjuvant chemotherapy as described in table 3 which is further classified into monotherapy and combinational therapy. Paclitaxel or zoledronic acid was the highest prescribed drug in each of 19 patients (14.5%) while Carboplatin, Fulvestrant, Ibandronic acid or Gemcitabine was the lowest prescribed drugs in each of 1 patient (0.8%) as monotherapy. Similar results were obtained in the study of “The Efficacy of Taxane Chemotherapy for Metastatic Breast Cancer in BRCA1 and BRCA2 Mutation Carriers” by Mike k, Agnes j, Maartje J H, Jabber B that most of the patients were prescribed with paclitaxel.[12]

Table 3: Distribution of drug based on adjuvant therapy

| Drug type     | Drug name                                  | Number of patients (n=131), (%) |
|---------------|--------------------------------------------|---------------------------------|
| Monotherapy   | Carboplatin                                | 01 (0.8%)                       |
|               | Fulvestrant                                | 01 (0.8%)                       |
|               | Gemcitabine                                | 01 (0.8%)                       |
|               | Ibandronate                                | 01 (0.8%)                       |
|               | Nab-paclitaxel                             | 02 (1.5%)                       |
|               | Paclitaxel                                 | 19 (14.5%)                      |
|               | Trastuzumab                                | 18 (13.7%)                      |
|               | Zoledronic acid                            | 19 (14.5%)                      |
| Combination therapy | 5-Flurouracil + Epirubicin, Cyclophosphamide | 04 (3.1%)                      |
|               | Cyclophosphamide + Fulvestrant            | 01 (0.8%)                       |
|               | Cyclophosphamide + Zoledronic acid        | 01 (0.8%)                       |
|               | Cyclophosphamide + Trastuzumab            | 03 (2.3%)                       |
|               | Docetaxel + Carboplatin + Trastuzumab     | 01 (0.8%)                       |
|               | Docetaxel + Tamoxifen                      | 01 (0.8%)                       |
|               | Doxorubicin + Cyclophosphamide            | 02 (1.6%)                       |
|               | Letrozole + Palbociclib                    | 03 (2.3%)                       |
|               | 5-Flurouracil + Epirubicin, Cyclophosphamide + Zoledronic Acid + Letrozole | 01 (0.8%)               |
|               | Fulvestrant + Cyclophosphamide + Zoledronic Acid | 02 (1.6%)               |
|               | Paclitaxel + Letrozole                     | 04 (3.1%)                       |
Cyclophosphamide + Docetaxel was the highest prescribed drug in each of 20 patients (15.3%). Cyclophosphamide + Fulvestrant; Cyclophosphamide + Zoledronic acid; Docetaxel + Carboplatin + Trastuzumab; Docetaxel + Tamoxifen; 5-Fluorouracil + Epirubicin + Cyclophosphamide + Zoledronic Acid + Letrozole; Tamoxifen + Zoledronic Acid; Trastuzumab + Capecitabine; Zoledronic Acid + Fulvestrant; Zoledronic Acid + Fulvestrant + Palbociclib; Cyclophosphamide + Docetaxel + Doxorubicin; Cyclophosphamide + Docetaxel + Trastuzumab + Letrozole; and Cyclophosphamide + Docetaxel + Paclitaxel were the lowest prescribed drugs in each of 1 patient (0.8%) as combination regimen. A similar finding was found on the study “adjuvant therapy for breast cancer: practice patterns of community physicians” by Linda C H, Jeffrey A, Joan L W, Lin C, Jennifer S that the combination regimen used was

- **TC** (Cyclophosphamide + Doxorubicin) q3week* 6cycles
- **FEC** (5-fluorouracil + Epirubicin + Cyclophosphamide) q3week* 4 cycles
- **CMF** (Cyclophosphamide + Methotrexate + Fluorouracil) q3week* 4 cycles
- **TAC** (paclitaxel + Adriamycin + cyclophosphamide) q3week* 4 cycles
- **Ac** (Adriamycin + cyclophosphamide) q3weeks *4 cycles
- **AC → Paclitaxel** (Adriamycin + cyclophosphamide, Paclitaxel) q3week* 4 cycles
- **CAF** (Adriamycin + cyclophosphamide + 5-fluorouracil) q3week* 6cycles
- **CEF** (Cyclophosphamide + Epirubicin + Fluorouracil) q3week* 4 cycles.[13]

The most prescribed regimen in our study were FEC, TC, CT, AC Letrozole+ zoledronic acid, Epirubicin+ Cyclophosphamide.
Patients receiving neoadjuvant chemotherapy as described in table 4 which is further classified into monotherapy and combinational therapy. Based on mono-therapy in neoadjuvant treatment therapy, Trastuzumab was the highest prescribed drug in 04 patients (40.0%). Paclitaxel or zoledronic acid were the lowest prescribed drugs in each of the 01 patients (10%). Similar finding was found in the study conducted “Outcome After Neoadjuvant Chemotherapy in Elderly Breast Cancer Patients - A Pooled Analysis of Individual Patient Data from Eight Prospectively Randomized Controlled Trials” by Waldenfels G, Loibl S, Furlanetto J, Machleidt A, Lederer B, Denkert C stated the Trastuzumab or Taxanes were the highly prescribed drug.[14] Based on regimen therapy in neoadjuvant treatment therapy, Cyclophosphamide + Docetaxel and Cyclophosphamide+ Epirubicin were the prescribed drug in each of the 02 patients (20.0%). Similar results was seen in the study on “Outcome of Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer: A Tertiary Care Center Experience” by Rahman MS, Akhter PS, Hasanuzzaman M, Rahman J, Bhattacharjee A, Russell M that Cyclophosphamide 600mg/m2 and Doxorubicin 60mg/m2 (AC) was prescribed and carried out three weekly for four cycles.[15]

### Table 4: Distribution of drug based on neoadjuvant therapy

| Drug therapy type   | Drug name                        | Number of patients (n=10), (%) |
|---------------------|----------------------------------|-------------------------------|
| Monotherapy         | Paclitaxel                       | 01 (10%)                      |
|                     | Trastuzumab                      | 04 (50%)                      |
|                     | Zoledronic Acid                  | 01 (10%)                      |
| Combination therapy | Cyclophosphamide + Docetaxel     | 02 (20%)                      |
|                     | Cyclophosphamide + Epirubicin    | 02 (20%)                      |

### Table 5: Distribution of drug based on palliative therapy

| Drug therapy type   | Drug name                                | Number of patients (n=37), (%) |
|---------------------|------------------------------------------|-------------------------------|
| Monotherapy         | Carboplatin                               | 01 (2.7%)                     |
|                     | Gemcitabine                               | 01 (2.7%)                     |
|                     | Paclitaxel                                | 02 (5.4%)                     |
|                     | Trastuzumab                               | 02 (5.4%)                     |
|                     | Zoledronic Acid                           | 17 (45.9%)                    |
| Combination therapy | Fulvestrant + Cyclophosphamide + Zoledronic Acid | 01 (2.7%)                     |
|                     | Paclitaxel + Zoledronic Acid              | 02 (5.4%)                     |
|                     | Tamoxifen + Zoledronic Acid               | 01 (2.7%)                     |
|                     | Trastuzumab + Zoledronic Acid             | 01 (2.7%)                     |
|                     | Zoledronic Acid + Palbociclib             | 01 (2.7%)                     |
|                     | Zoledronic Acid + Letrozole               | 08 (21.6%)                    |
Patients receiving palliative chemotherapy as described in table 5 which is further classified into monotherapy and combinational therapy. Zoledronic acid was the highest prescribed drug in 17 patients (45.9%) while Carboplatin or Gemcitabine was the lowest prescribed drug in each of 1 patient (2.7%) as monotherapy. Zoledronic acid + Letrozole was the highest prescribed drug in 02 patients (5.4%). Fulvestrant+ Cyclophosphamide+ Zoledronic Acid; Tamoxifen + Zoledronic Acid; Trastuzumab + Zoledronic Acid; and Zoledronic Acid + Palbociclib were the lowest prescribed drugs in each of 01 patient (2.7%) as combination therapy.

The majority of patients had received premedication like granisetron, dexamethasone, pantoprazole, calcium supplement, zolpidem, ranitidine, paracetamol to reduce the side effects of associated chemotherapeutic drugs. However small fractions of side effects were observed like back pain (1.1%), anxiety (0.6%), anemia (0.6%), neutropenia (1.1%), dry cough (1.1%), myalgia (1.1%).

CONCLUSION:
The most commonly diagnosed invasive cancer among women is breast cancer. It is the second leading cause of death in women, accounting for 25.1% of all cancers. Adjuvant chemotherapy was given to a higher number of patients as they usually get admitted after breast surgery. The most common adjuvant therapy used as monotherapy was paclitaxel, zoledronic acid, trastuzumab. The most common adjuvant therapy used as combination regimens were Cyclophosphamide + docetaxel (TC). The most common neoadjuvant therapy used as monotherapy was trastuzumab. The most common adjuvant therapy used as combination regimens were cyclophosphamide + Docetaxel (TC) and Cyclophosphamide + Epirubicin. The most common palliative therapy used as monotherapy was Zoledronic acid. The most common palliative therapy used as combination regimens was Zoledronic acid + Letrozole. The side effects observed in the study were anxiety, back pain, anemia, dry cough, myalgia.

The most prescribed drugs were paclitaxel, trastuzumab, cyclophosphamide + docetaxel, 5 fluorouracil + epirubicin + cyclophosphamide, epirubicin + cyclophosphamide, and zoledronate found to be more effective and safer drugs than other regimens. Few patients did not undergo medication adherence and switch to other regimens due to the high cost of prescribed medication. The selection of chemotherapeutic drugs requires enough knowledge about the drug and the patient’s condition.

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