EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 9
380-389
Year: 2020

EVALUATION OF CHEMOTHERAPEUTIC AGENT AMONG BREAST CANCER RECEIVING CHEMOTHERAPY; AN OBSERVATION PROSPECTIVE STUDY

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Article Received on 20/07/2020 **Article Revised on 10/08/2020** **Article Accepted on 30/08/2020**

ABSTRACT

Objectives: This hospital based case study was undertaken with aim to evaluation of chemotherapeutic agents in management of carcinoma management of breast in oncology specialized hospital. the objective of this study was to assess prescribing patterns of breast cancer and to determine rational use and appropriate choice of chemotherapevlic aged is depends on type and grade of cancer and also patient specific characteristic according to NCC guideline and EVIQ guideline. **Methods:** The study was a prospective observational study which was carried for a period of 6 months in Bharath Hospital in patients with breast cancer receiving chemotherapy. Most of the patient details were collected from patient case sheets or laboratory reports. A total of 100 patients who were receiving anti-cancer agent as either adjuvant or neoadjuvant therapy for breast cancer followed during 6 month of study period. In this study appropriateness/ inappropriateness of chemotherapy regimen were reviewed base on their indicated stage, dose, route, and frequency duration of administration. **Results:** the result of study found inappropriate as per NCCN and EVIQ guideline. **Conclusion:** based on current findings, it can be suggested that uses of anti-emetic drugs need further improvement in terms of frequency and choice of drug in many cases. Education and training program to nursing staff would certainly help to improvise the delivery of chemotherapy.

KEYWORDS: Chemotherapy, Drug utilization, Endocrine therapy.

INTRODUCTION

Breast cancer is a type of cancer that develops from breast tissue.[1] A cancer that arising in the epithelial tissue of the skin or of the internal organs lining is called Breast Carcinoma. Worldwide, breast cancer is the most common invasive cancer in women.[2] It affects about 12% of women worldwide.[2] Breast cancer comprises 22.9% of invasive cancers in women[3] and 16% of all female cancers.[4] In 2012, it comprised 25.2% of cancers diagnosed in women, making it the most common female cancer[5] that caused 458,503 deaths worldwide In 2008 (13.7% of cancer deaths in women and 6.0% of all cancer deaths for men and women together).[3] In India, over 100,000 new breast cancer patients are estimated to be diagnosed annually.[17] According to ??? disease pattern and presentation of breast cancer in India is differs from the West.[18]

In Adjuvant and Neo adjuvant therapy, Chemotherapy plays a major and very important role in management of breast cancer which are administered concurrently or in specified sequential regimens followed by hormonal therapy in patients with hormone positive breast cancer.

Several studies were conducted to determine the rational use of chemo regimen in management of breast cancer and came out with few findings that are as follows:[18]

In case of inappropriate use of chemotherapy regimens, several studies determined that it may lead to huge drug wastage; thereby drug shortage, unnecessary adverse drug reactions, increased drug resistance and increases unnecessary cost of treatment. Also, there arises a potential mistrust on the real efficacy of chemotherapy due to its use for inappropriate indications. A drug utilization evaluation study can help us in understanding the prescribing patterns of a drug and possibly the factors influencing the prescribing. Drug use evaluation is an ongoing, systematic, quality improvement process within a healthcare organisation. Implementation of DUE helps to improve the quality and cost-effectiveness of the drug use thereby improving the patient care. In recent years, studies on drug utilization have become a potential tool for the evaluation of health systems. The first and foremost aim of drug utilization evaluation is patient care through optimization of drug therapy. This can be achieved through the ongoing review of use of a drug and other data in a given health care environment.[18] Hence, it was felt essential to systematically review the

utilization patterns of chemotherapeutic agents used as adjuvant and neo-adjuvant therapy in the management of breast cancer with respect to standard international recommendations to improve the prescribing pattern and thereby promote rational use of chemotherapy regimens in management of breast cancer.

Chemotherapy is used as a neoadjuvant treatment to make it easier to remove the cancer. Also, chemotherapy are used to shrink tumors larger than 5 cm that would be otherwise unfit for surgery. Otherwise, chemotherapy is used as an adjuvant treatment for early-stage breast cancer. In metastatic breast cancer, the goal is to control the cancer so that patient can live longer with the best quality of life possible. Chemotherapy is administered in two ways, orally as a pill and intravenously. Sometimes chemotherapy is one drug is used, called a single agent. Other times a combination of drugs is used it is called as chemotherapy regimen. Cancer chemotherapy may be indicated as a primary, palliative, adjuvant, or neoadjuvant treatment modality. The goals of chemotherapy are cure, control and palliation and treatment goal of chemotherapy is used to decide which chemotherapy drug(s) should be used. A protocol plan is drawn up which specifies when treatment sessions will occur and for how long.

2. MATERIALS AND METHODS

2.1 Study Site

The study was conducted at Bharath Hospital & Institute of Oncology (BHIO). It is a belonging to HealthCare Global (HCG) Enterprises Ltd, the specialist in cancer care. It is a cancer care network with quality care across 27 centres in India. The hospital has various services like medical oncology, surgical oncology, radiation oncology, palliative care and social worker services. Generally, on outpatient basis around 100 patients receive care on daily basis and around 20 new patients will be admitted for diagnosis, follow up and treatment purpose.

Study Design

This was a prospective observational study that was carried out for a period of six months September 2016 to February 28th 2017.

Ethical Approval

Institutional Human Ethical Committee.

Study Procedure

The study involved the following steps:-

1. Preparation of informed consent form (ICF)

An informed consent form was suitably designed both in English (Annexure-I) and Kannada (Annexure-II) to obtain consent from patients who volunteered for the study and fulfilled the study criteria. The ICF was reviewed and approved by an institutional ethics committee. The patient was, explained about the study and asked to sign the ICF. If the patient was illiterate, the ICF was to be signed by an impartial witness.

2. Preparation of data collection form

A specially designed data collection form (Annexure-III) was devised for the study. The particulars included demographic details like name, age, gender, family history, social habits, diet, height, weight, body surface area, address,; clinical data such as diagnosis, past medication history, co-morbidities, allergy status, tumor size, stage of disease therapeutic data such as name of the drug, dose, frequency, route, and duration of administration, concurrent medication(s), laboratory tests and results. The same details were documented electronically in specially designed database using Microsoft access 2010. To report, document and assess adverse drug reactions due to anti-cancer drugs used for treatment of breast cancer, standard documentation form of clinical pharmacy department Sarada Vilas College of Pharmacy, Mysore.

3. Patient enrollment

Patients fulfilling the study criteria were enrolled into the study after obtaining the informed consent. Patients were enrolled from in-patients general wards, private wards and day care center.

Data collection

All relevant details of the enrolled patients were obtained from various data sources and documented in the data collection form.

4. Assessment of utilization chemotherapeutic agents in the hospital

Utilization evaluation of chemotherapeutic agents as adjuvant and neo-adjuvant therapy was conducted on qualitative basis. All the enrolled patients were reviewed in terms of chemotherapy regimen prescribed and anti-emetics recommended. Clinical stage of the disease, tumor characteristics, drug selection, dose, route, administration technique and anti-emetics used were reviewed with respect to standard international recommendations to evaluate the appropriateness of the chemotherapy and anti-emetics used. To evaluate appropriateness of chemotherapy regimen and anti-emetics prescribed National Comprehensive Cancer Network (NCCN) guidelines were used as a standard and to evaluate appropriateness of administration technique, guidelines from Cancer Institute New South Wales, Australia (available at https://www.eviq.org.au/) were considered as a standard.

5. Monitoring, evaluation and documentation of adverse drug reactions to anti-cancers

All patients enrolled in the study were monitored for occurrence of adverse reactions to chemotherapeutic agents. On identification of ADR, all necessary data was collected and documented in the ADR documentation form. Causality of the ADRs was assessed using the WHO ADR probability scale and Naranjo's algorithm The reported ADRs were also assessed for their severity by using the Modified Hartwig and Siegel scale The predictability of the reported reactions was estimated

using the predictability scale and preventability by the Modified Shumock and Thornton criterion.

3. RESULTS

3.1. Demographics and other patient information

Breast cancer was found more common (n=55, 55%) among age group 50-69 years followed by 36-49 years (n=27, 27%), ≤ 35 years (n=13, 13%). Only few patients (n=5, 5%) were of age 70 and above. All the patients (n=100,100%) followed during study were female and did not have family history (first degree relative) of breast cancer. Among all patients majority of them were purely vegetarian (n=76, 76%) and remaining (n=24, 24%) were following mixed diet. Most of the patients were married (85%) and remaining were unmarried (5%) and widows (10%).

Looking at the menstrual history of the patients, all the patients had their first menses during age 11-14 years and none of the patients had any known menstrual irregularity before the diagnosis of breast cancer. Menopausal status of the patients was found with almost equal distribution i.e. 49 of 100 patients were in pre-menopausal stage and remaining 51 of 100 were in post-menopausal stage. Of 100 patients, 93 of them had their first pregnancy at the age of 30 or below. Among remaining patients, 5 of them were nulliparous and 2 of them had their first pregnancy at the age between 30-35 years.

Table 2: Tumour characteristics.

Tumour characteristics	Number of patients	Percentage
Involvement of breast:		
Left	46	46
Right	52	52
Both	02	2
Infiltrating:		
Lobular	--	--
Ductal	46	46
Invasive:		
Lobular	9	9
Ductal	36	36
Metastatic	9	9
Stages of breast cancer:		
Stage 0	06	06
Stage IA	07	07
Stage IIA	19	19
Stage IIB	07	07
Stage IIIA	26	26
Stage IIIB	04	04
Stage IIIC	23	23
Stage IV	08	08
Hormonal receptor status:		
Estrogen receptor:		
Positive	18	18
Negative	69	69
Not done	13	13
Progesterone receptor:		
Positive	16	16
Negative	71	71
Not done	13	13
HER2 gene test:		
Positive	06	06
Negative	75	75
Not done	13	13
Equivocal	06	06

Table 3: Recommended treatment for Breast Cancer.

Recommended Treatment	Number of patients	Percentage of patients
Adjuvant	78	78
Neo-adjuvant	17	17
Palliative	05	5
Radiation (concomitant with chemotherapy)	34	34

Table 5.3: Appropriateness of chemotherapeutic agents used:		
FEC Regimen		
	Appropriate	Inappropriate
Indicated as per stage	11(100%)	--
Dose	08 (72.72%)	03 (27.27%)
Route	11(100%)	--
Frequency	11(72.72%)	--
Administration	07 (63.63%)	04 (36.36%)
Anti-emetic drugs used	09 (81.81%)	02 (18.18%)
FEC Docetaxel Regimen		
	Appropriate	Inappropriate
Indicated as per stage	03(100%)	--
Dose	03(100%)	--
Route	03(100%)	--
Frequency	03(100%)	--
Administration	03 (100%)	--
Anti-emetic drugs used	03 (100%)	--
Paclitaxel-A		
	Appropriate	**Inappropriate**
Indicated as per stage	06 (100%)	--
Dose	06 (100%)	--
Route	06(100%)	--
Frequency	06 (100%)	--
Administration	04 (66.66%)	02 (33.3%)
Anti-emetic drugs used	06 (100%)	--

Paclitaxel Single therapy		
	Appropriateness	**Inappropriate**
Indicated as per stage	1(100%)	--
Dose	1(100%)	--
Route	1(100%)	--
Frequency	1(100%)	--
Duration	1(100%)	--
Administration	--	1(100%)
Anti-emetic drug used	**1(100%)**	--

Appropriateness/inappropriateness of the chemotherapy regimens were reviewed based on their indicated stage, dose, route, frequency, duration, administration and adjunct anti-emetics used considering NCCN recommendations for treatment of breast cancer and management of chemotherapy induced nausea and vomiting and https://www.eviq.org.au/ recommendations for administration guidelines while using anti-cancer and anti-emetics used for patients of breast cancer. The detailed findings are given in table 5.

Table 6: Treatment of Breast Cancer in the patients with Endocrine Responsive Tumor.

Receptor Status	**Number of Patients**	**Treatment**		
		CT+ET	**CT**	**ET**
ER Positive	18	16 (16%)	**02 (2%)**	--
ER Negative	69	--	69(69%)	--
ER status not known	13	**05 (5%)**	08(8%)	--
PR Positive	16	16 (18.18%)	--	--
PR Negative	71	--	71 (71%)	--
PR Status not known	13	**04 (4%)**	09(9%)	--

ER: Estrogen receptor, PR: Progesterone receptor, CT: Chemotherapy, ET: Endocrine Therapy

Out of 100 patients reviewed, 18 patients had ER positive tumor and 69 patients had ER negative tumor. However, ER and PR response of 13 patients was not known. Of 100 patients, 16 of them were positive to PR and 71 of them were negative. Of 18 patients with ER positive status 16 of them received chemotherapy and endocrine therapy both whereas remaining 2 patients received only chemotherapy and no endocrine therapy. 5 of 13 patients with unknown ER response status received chemotherapy and endocrine therapy both whereas

remaining 8 of 13 patients received only chemotherapy. All 16 patients with PR positive status received chemotherapy along with endocrine therapy. However, 4 of 13 patients with unknown PR response status also received chemotherapy along with endocrine therapy.

Table 7: Treatment of HER2 Positive Breast Cancer.

Receptor status	Number of patients	Treatment Given		
		CT+TT	CT	RT
HER2 Positive	06	02 (2%)	04 (4%)	--
HER Negative	75	--	75 (75%)	22
HER2 Not Performed	13	--	13 (13%)	13
HER2 equivocal	06	--	06 (6%)	--

CT: Chemotherapy. TT: Targeted Therapy, RT: Radiation therapy

Out of 100 patients, 6 patients were HER2 positive and only 2 of them received chemotherapy with targeted therapy (Transtuzumab) whereas other patients received chemotherapy without targeted therapy. 6 of 87 patients tested for HER2 gene were on equivocal status and they were not repeated to perform the test again and they did not receive targeted therapy.

Table 8: Endocrine Therapy used for Hormone responsive Tumor.

Patient menopause status	Endocrine therapy used	Appropriate	Inappropriate
Pre-menopausal state	Tamoxifen 20mg for 5 years	10 (24.39%)	--
Post-menopausal state	Anastrozole 1mg for 5 years	22 (53.65%)	--
	Letrozole 2.5mg for 5years	19 (46.34%)	--

All the pre-menopausal patients with endocrine responsive tumor were prescribed with Tamoxifen (n=10, 24.39%) oral tablet for 5 years and post-menopausal patients were prescribed with anastrozole (n=22, 53.65%) and letrozole (n =19, 46.34%) oral tablet respectively.

Adverse drug reaction reported to chemotherapy agents

A total of 117 ADRs were reported in 79 patients who received chemotherapy. Number of ADRs found were higher (n=60, 51.28%) in age group 50-69 years followed by 39 (33.33%) ADRs in age group of 36-49 years, 10 ADRs in patients of age 35 or younger and 8 ADRs were reported in patients aged 70 and above. Majority of ADRs to chemotherapy were found due to AC regimen, FAC regimen, AC Paclitaxel regimen and FEC regimen. Details of ADRs reported with suspected drugs are given in Table. As per WHO probability scale and Naranjo's scale most (94.01%) of the ADRs were found to be *'Probable' and Probable* in nature respectivelyand 6% of ADRs were found to be *'Possible'.* Among 117 ADRs, 84 (71.79%) ADRs were 'mild' [level1, level2] in nature and 33 (28.20%) ADRs were 'moderate' [level3, level4 (a)]. No ADR was found to be severe in nature. Of the 117 ADRs, 110 (94.01%) were 'Predictable' and 7 (5.98%) were 'Not predictable'.

Table 9: Adverse drug reactions reported to chemotherapeutic agents used.

Prescribed Regimen	ADRs (n)	Name of ADR (n)	Suspected Chemotherapeutic agent
AC Regimen	47	Alopecia(26)	Doxorubicin+Cyclophosphamide
		Vomiting (16)	Doxorubicin+Cyclophosphamide
		Neutropenia (1)	Doxorubicin
		Discoloration of tongue, nail (3)	Cyclophosphamide
		Stomatitis (1)	Cyclophosphamide
AC-Paclitaxel	16	Alopecia (1)	Doxorubicin+Cyclophosphamide
		Vomiting (6)	AC+ Paclitaxel
		Leucopenia (2)	Paclitaxel
		Neuropathic pain (2)	Paclitaxel
		Myalgia (4)	Paclitaxel
		Thrombocytopenia (1)	Paclitaxel
FAC	25	Hyperpigmentation of skin (11)	Fluorouracil
		Vomiting (7)	Doxorubicin+Cyclophosphamide
		Alopecia (5)	Doxorubicin+Cyclophosphamide
		Leucopenia (1)	Cyclophosphamide
		Discoloration of tongue, nails (1)	Cyclophosphamide
FAC Paclitaxel	03	Myalgia (1)	Paclitaxel
		Neutropenia(1)	Cyclophosphamide

		Leucopenia (1)	Paclitaxel
FEC	09	Hyperpigmentation of skin (7)	Fluorouracil
		Alopecia (1)	Epirubicin+Cyclophosphamide
		Neutropenia(1)	Cyclophosphamide
FEC Docetaxel	01	Hyperpigmentation of skin (1)	Fluorouracil
TAC	09	Myalgia (5)	Docetaxel
		Alopecia (1)	Doxorubicin+Cyclophosphamide
		Leucopenia (1)	Docetaxel
		Rashes (2)	Doxorubicin
CMF	02	Hyperpigmentation of skin (2)	Fluorouracil
TA	01	Alopecia (1)	Doxorubicin
		Leucopenia (1)	Docetaxel
EC	03	Leucopenia (1)	Cyclophosphamide
		Discoloration of tongue, nails (2)	Cyclophosphamide
Docetaxel Single	01	Myalgia (1)	Docetaxel

Table 10: Pre-medications used with chemotherapy.

Name of the regimen	Drugs used as Pre Medication in No of Patients
AC	Ondansetron + Dexamethasone (n=15, 45.45%)
	Palanosetron + Dexamethasone -17 (51.51%)
	Dexamethasone+Ondansetron-1 (3.03%)
AC-Paclitaxel	Dexamethasone+Ondansetrone+Ranitidine-2(25%)
	Palanosetrone+Dexamethsone+Pantoprazole-1 (12.5%)
	Ondansetrone+Dexamethasone-3 (37.5%)
	Pantoprazole+Dexamethsone+ Ondansetrone-1 (12.5%)
	Aprepitant+ Dexamethasone-1 (12.5%)
FAC	Ondansetrone-8 (47.05%)
	Dexamethasone-1 (5.88%)
	Dexamethsone+Pantoprazole-2 (11.76%)
	Dexamethasone+Ondansetrone-1 (5.88%)
	Palanosetrone+Dexamethsone-1 (5.88%)
	Palanosetrone-4 (23.52%)
FEC	Dexamethasone+Ondansetrone-1 (12.5%)
	Ondansetrone-8 (25%)
	Palanosetrone+Dexamethsone+Pantoprazole-1 (12.5%)
	Palanosetrone-5 (62.5%)
	Palanosetrone+Dexamethsone+Ranitidine-1 (12.5%)
FEC-Docetaxel	Ondansetron+Dexamethasone+ Fosaprepitant-2 (66.66%)
	Dexamethasone+Ondansetron-1 (33.33%)
TAC	Ondansetron +Dexamethsone+Ranitidine-1 (12.5%)
	Palanosetrone+Dexamethsone+Pantoprazole-1 (37.5%)
	Ondansetrone+Dexamethsone+Pantoprazole-1 (12.5%)
	Dexamethasone+Ondansetrone-2 (25%)
	Ondansetron +Aprepitant+ Dexamethasone-1 (12.5%)
CMF	Metoclopramide -3 (100%)
TA	Palanosetrone+Dexamethsone+Pantoprazole-1 (100%)
EC	Palanosetrone-2 (50%)
	Ondansetrone-2 (50%)
Docetaxel	Palanosetrone+Dexamethsone+Pantoprazole-1 (100%)
Paclitaxel	Palanosetrone+Dexamethsone+Pantoprazole-1 (100%)

Pre-medications of the patients were reviewed considering chemotherapy regimen prescribed, with respect to NCCN guidelines. Table 10 shows chemotherapy regimen and pre-medications used along with it.

DISCUSSION

Cancer remains a major health burden in the developing world. Chemotherapy, over the years, have been used in an attempt to reduce the morbidity rates, recurrence rates and increase the survival rates of breast cancer patients. This, however, has resulted in its imprudent use and associated consequences of increased resistance to

chemotherapy treatment, unnecessary adverse reactions and inappropriate management of patients.[4]

This work is focussed on assessing the utilization patterns of chemotherapy drugs used in the management of breast cancer at our study site. For early stages and in advanced stages adjuvant therapy are used and in very advanced stages and at late stages neo adjuvant therapy are used. The selection of therapy among these two were completely appropriate based on tumour size and as per TNM classification.

In our study, we tried to relate the risk of patient characteristics (age, gender, family history, menstrual status, pregnancy, marital status) ages 50-69 (55%) were at high risk of developing breast cancer which is relating to a study that showed patient younger than 60 have an 80% risk of developing breast cancer.

In our study there is no family history of getting a breast cancer similarly other studies revealed only 5% have reported a low rate of familial pattern of breast cancer in Indian patients. It indirectly shows that Genetic screening/ diagnosis is not routinely performed in most Indian centers due to paucity of funds and facilities.

Menstrual history is also a identifiable risk factor of breast cancer. Hence in our study we recorded detail information of patient regarding age of menses, menstrual abnormalities, menopause status and age of pregnancy. In our study we identified full (n=100, 100%) of the current patients had their first menarche at an age older than 11 years, and all were placed in a low risk category. According to Sprague *et al.* women who were younger at menarche (≤12 years) are at an increased risk of developing breast cancer because long menstrual history increases life time exposure to oestrogen.[23]

According to a study, women who are older at menopause (>55 years) are at an increased risk of developing breast cancer (Sprague et al.,) because long menstrual history increases life time exposure to oestrogen.[23] In Asian women menopausal status was, however, not associated with breast cancer risk (Wu et al.,).[24] Similar to this study, In our study not a much difference in numbers we noticed, between the pre menopause(n=49, 49%) and post menopause(N=51, 51%) women as Indian women attains menopause at the age between 48-52 years.

The treatments of breast cancer are decided only after the stage of breast cancer is diagnosed. Hence, if the staging is inappropriately diagnosed the chances of failure of treatment are high. In our study we noticed a high number of advanced stages i.e., Stage IIIA cases (n=26, 26%) followed by Stage IIIC cases (n=23, 23%). These numbers are high mainly because of relapse even after receiving chemotherapy treatment and patients who received Ayurveda treatment before and later the patient had come to oncology hospital for further treatment, by this time the disease got progressed. Whereas, when it comes to early stages like stage 0 (n=6, 6%) and stage 1A (n=7, 7%) the numbers are quite less. It doesn't mean that breast cancer cases got reduced, it is mainly because of lack of awareness, lack of education regarding breast cancer and hence the patients come to hospital either at advanced stage or late stage.

In this study we noticed more number of triple negative cases above 70% this finding was similar to a study were above 50% of cases were reported.[25] The triple negative cases did not receive any kind of endocrine therapy, as it will be ineffective in cases of triple negative breast cancer.

The treatment of breast cancer is based on mainly two types i.e., adjuvant and neo adjuvant, in cases of very late stage palliative treatment has been done. In our study adjuvant (n=78, 78%) are more compared to neo adjuvant (n=17, 17%). The decisions regarding these therapies are usually decided by surgical oncologist, if the surgeon feels the tumour size is operable they will give adjuvant therapy and if they feel the tumour size not operable they will first prefer with chemotherapy after the tumour get shrinked next operation will be done i.e. neo adjuvant. Here, radiation therapy (n=34, 34%) was received along with adjuvant and neo adjuvant therapy, depending upon the decision made by radiation oncologist, the number of fractions and amount of gray of radiation has been given.

Our study showed a high rate of prescribing, various combination of chemotherapy regimens at stage 3A and stage 3C. Among all chemotherapy regimens AC regimen (n=34) were given in all the stages compared to the other chemotherapy regimens even thou it is not preferable at very advanced stage as per standard guidelines, because Govt approves this regimen at free of cost for economically poor patients. Whereas, Govt and many other insurance schemes will not approves financial aids to the costly chemotherapy regimen. Therefore many times with no choice oncologist prefer AC regimen even if it is not appropriate in that particular stage of breast cancer. The selection of chemotherapy regimen decision is done by oncologists by considering various factors like age, economic status, stage of the disease, hormone receptor status Etc.

To carry out utilization and evaluation of chemotherapy regimens, we compared the present prescribing pattern of our study site with the NCCN and EVIQ online as these, both guidelines are globally well accepted and practiced in the treatment of breast cancer. Our main focus was on to identify, the appropriateness and inappropriateness of chemotherapy regimen prescribed as per the stage, dose, frequency, administration techniques, route and anti emetics used as pre medications by comparing with the NCCN and EVIQ guidelines. By following this comparisons process, we noticed more inappropriateness, like chemotherapy regimens were prescribed not as per

the stage, the doses of chemotherapy drugs were high. This is mainly because the body surface area was not calculated regularly. Here in our study site, the dose was fixed according to the first cycle of chemo, as patients receives further chemo treatment as per scheduled dates, the weight of the patient will reduce due to adverse effects of chemotherapy treatment. As the weight reduces the calculation of body surface area also varies and the dose will be overdose. The timing of administration and infusion were also inappropriate in terms of AC-Paclitaxel regimen, Paclitaxel should be given for 3hrs, but in our study site it has been administered with in 1hr and in terms of FAC and FEC regimens the infusion of 5FU and Doxorubicin should be mixed in 100ml of NS, but in our study site it was done in 500ml NS and the reason given by the oncologist is, the availability of glass container 100ml NS is less and they don't want to mix the chemo drug in 100ml NS plastic container as it may lead to interaction between plastic container and chemo drugs. But, this practice leads to over dilution of drug and desired therapeutic effects may not be reached. The anti-emetics used as pre medications were identified as not appropriate as per the guidelines and this has led patients to have more side effects like vomiting, nausea. The high emetogenic drugs like cyclophosphamide, paclitaxel and docetaxel were prescribed with metaclopropamide instead of 5 HT3 antagonists like ondansetrone, palanosetrone etc and only in 2 cases NK1 receptor antagonist i.e., Aprepitant were used as this drug is costly, so it was given only in case of affordable patients. Even if the choice of the anti-emetic is appropriate, but the dose prescribed were inappropriate like patients receiving CMF, FAC, FEC regimens received anti-emetic ondansetron 16mg IV and had vomiting episodes. As per guidelines ondansetron 32mg IV is advised.

It is necessary to give endocrine therapy, if the patient were found to be positive in case of oestrogen and progesterone and if it is untreated this may lead to the recurrence of disease and reduce the survival rate. In our study for Oestrogen (n=18,18%) and Progesterone (n=16,16%) positive cases are less compared to the negative cases Oestrogen (n=69,69%) and Progesterone (n=69,69%) and in 13 cases of both progesterone and oestrogen, the hormone receptor status tests were not performed because of two reasons, one is if lumpectomy has been performed then the sample for biopsy to conduct hormone receptor test will not be available and if patients are late stage and receiving palliative therapy these tests will not be performed, as it increases the cost of treatment and those patients who were positive for hormone test received endocrine therapy, But still in our study site, those patients whose hormone status were not known were prescribed with endocrine therapy i.e., in Oestrogen 5 patients and in case of progesterone 4 patients received endocrine therapy along with chemotherapy these kind of prescribing pattern is carried out mainly by oncologist clinical practice experience. But, we noticed this practice is inappropriate when compared to NCCN and EVIQ guidelines.

HER2 is over-expressed in 15–20% of invasive breast carcinomas. HER2 expression is an individual prognostic factor for predicting the aggressive behaviour of the tumour as well as the benefit from adjuvant therapy. Trastuzumab suppresses HER2 activity, thereby facilitating apoptotic cell death. Clinical trials have shown that the relative risk of recurrence is decreased by 50% when trastuzumab is added to the adjuvant chemotherapy regimen in HER2-positive women. In addition, trastuzumab significantly prolongs survival in HER2-positive metastatic breast cancer patients. Therefore, it is important to accurately assess the HER2 status for patients who may benefit from targeted therapy. In our study we identified positive case (n=6), negative cases (n=75), No of cases where test was not performed (n=13) and equivocal cases were (n=6). Among positive cases of 6 only 2 patients received chemotherapy and trastuzumab drug, whereas remaining 4 received only chemotherapy treatment as trastuzumab is very expensive and under Govt, ESI and other insurance schemes this trastuzumab regimen cannot be claimed. The negative cases (n=75) received only chemotherapy as per guidelines this was found to be appropriate. 13 patients were not performed this test due to late stage and lumpectomy process. The equivocal cases (n=6) were not repeated with FISH technique as it will give clear picture of positive or negative. As this technique is expensive, hence it is not performed.

The choice of endocrine therapy should be correct, to stop the over expression of estrogen and progesterone. In case of postmenopause status, tamoxifen drug will be ineffective, but in case of pre menopause it is effective. Similar findings were identified in our studies the use of endocrine therapy in pre and post-menopausal women 55.5% women received tamoxifen and 44% received anastrazole and letrozole which were found appropriate as per the guidelines.

The prescribed anticancer drugs in treatment of breast cancer, were belonged to the various classes of cytotoxic drugs like 5FU is antimetabolite, cyclophosphamide is an alkylating agent. Each drug has various incidences causing different adverse effects. AC regimen has got more incidence (59%) of causing alopecia, darkening of nails. FAC and FEC regimen causes more hyperpigmentation of skin (80%) due to 5FU. Number of ADRs found were higher (n=60, 51.28%) in age group 50-69 years followed by 39 (33.33%) ADRs in age group of 36-49 years. In a study conducted at Bangladesh by Sneegdha Podar et al., (26%) reported that the patients of age group 41-50 years experienced more number of ADRs. In our study, more number of ADRS found in age group between 50-69 years. The reason of increased number of ADRs in this age group would be due to the reason that the metabolizing capacity and the excretory functions are generally diminished leading to

accumulation of drugs in the body and thus increasing the risk of ADRs in this age group and other risk factor is probably due to more number of chemotherapy cycles along with the progressing age.

The anti-emetics are mainly used to avoid side effects like nausea, vomiting and GI irritation, as this usually occurs during chemotherapy session. These side effects will reduce the quality life style of patients, thus patient's starts rejecting chemotherapy treatment during cycles of chemotherapy session. In this study, we assessed the use of anti-emetics practiced in the study site with the NCCN guidelines and eviQ and found that the anti-emetics are used inappropriately. The high emetogenic drugs like cyclophosphamide, paclitaxel were prescribed with low dose of dexamethasone and ondansetrone and moderate emetogenic drugs were prescribed with high dose of ondansetrone and dexamethsone. As per guidelines. NK1 receptor antagonists should be advised along high emetogenic chemotherapy regimen but in our study, we found that only 2 patients received aprepitant, as this costly this not prescribed regularly and also, the timing of administration of pre medications were inappropriate. In case of AC-Paclitaxel regimen previous night ranitidine 150mg tab will be prescribed, but in our study none of the who received paclitaxel used ranitidine tablet. In case of ondansetrone as per guidelines, it is given before 30min of chemotherapy, where as in our study we found that it has been administered just before chemotherapy infusion. This inappropriate practice may lead to severe side effects which we found in our ADR table that vomiting incidence is more.

CONCLUSION

The selection of chemotherapeutic agents was found in compliant with NCCN guidelines. However, administrations of these agents were concern due to inappropriate and inconsistent administration techniques followed. Uses of anti-emetic drugs need further improvement in terms of frequency and choice of drug in many cases. Dosing calculation of chemotherapeutic agents should be done based on latest body surface for subsequent cycle to avoid over dose or under dose. Education and training program to nursing staff would certainly help to improvise the delivery of chemotherapy. Inappropriate use of anti-emetics contributed for episodes of vomiting for few patients and same can be prevented with appropriate use of anti-emetics.

REFERENCES

1. "Breast Cancer". NCI. Retrieved 29 June 2014.
2. McGuire, A; Brown, JA; Malone, C; McLaughlin, R; Kerin, MJ (22 May 2015). "Effects of age on the detection and management of breast cancer.". Cancers, 7(2): 908–29.
3. "World Cancer Report". International Agency for Research on Cancer. 2008. Retrieved 26 February 2011. (Cancer statistics often exclude non-melanoma skin cancers such as basal-cell carcinoma, which are common but rarely fatal)
4. "Breast cancer: prevention and control". World Health Organization. Archived from the original on 6 September 2015.
5. World Cancer Report 2014. International Agency for Research on Cancer, World Health Organization. 2014. ISBN 978-92-832-0432-9.
6. Stewart B. W. and Kleihues P. (Eds): World Cancer Report. IARCPress. Lyon 2003Archived 20 October 2008 at the Wayback Machine.
7. Laurance, Jeremy (29 September 2006). "Breast cancer cases rise 80% since Seventies". The Independent. London. Archived from the original on 25 April 2008. Retrieved 9 October 2006.
8. "Breast Cancer: Statistics on Incidence, Survival, and Screening". Imaginis Corporation. 2006. Retrieved 9 October 2006.
9. Breast Cancer: Breast Cancer in Young Women WebMD. Retrieved 9 September 2009.
10. Nearly 85% of women diagnosed with breast cancer now survive for 5 year or more Office for National Statistics, 2013.
11. Olson, James Stuart (2002). Bathsheba's breast: women, cancer & history. Baltimore: The Johns Hopkins University Press. pp. 9–13.
12. "Oldest evidence of breast cancer found in Egyptian skeleton". Reuters. 24 March 2015. Retrieved 25 March 2015.
13. "The History of Cancer". American Cancer Society. 25 March 2002. Retrieved 9 October 2006.
14. Olson, James Stuart (2002). Bathsheba's breast: women, cancer & history. Baltimore: The Johns Hopkins University Press. pp. 32–33.
15. Yalom, Marilyn (1997). A history of the breast. New York: Alfred A. Knopf. p. 234.
16. Aronowitz, Robert A. (2007). Unnatural history: breast cancer and American society. Cambridge, UK: Cambridge University Press. pp. 22–24.
17. Vinodkumar Mugada, Aswinichand Paruchuri, Mounika Munagala. "Drug Utilization Evaluation of Anticancer Drugs in a Tertiary Care Teaching Hospital: a Descriptive Observational Study". *Journal of Applied Pharmaceutical Science, 2016; 6(10): 098-101, October,*
18. Samiya Abdul Saleem Khan, MohdIlyaz, K Manasa. Pharmacoepidemiological Trend and Drug Utilization Review of Breast Cancer at Three Different Tertiary Care Hospitals. *The Pharma Innovation Journal, 2015; 4(8): 12-18.*
19. Venur, Vyshak Alva; Leone, José Pablo (2016-09-13). "Targeted Therapies for Brain Metastases from Breast Cancer". *International Journal of Molecular Sciences, 17(9): 1543.*
20. Suryawanshi, Yogesh R.; Zhang, Tiantian; Essani, Karim (2017-02-09). "Oncolytic viruses: emerging options for the treatment of breast cancer". *Medical Oncology, 34(3): 43.*
21. Yu, Lin-Yu; Tang, Jie; Zhang, Cong-Min; Zeng, Wen-Jing; Yan, Han; Li, Mu-Peng; Chen, Xiao-Ping (2017-01-12). "New Immunotherapy Strategies in Breast Cancer". *International Journal of*

Environmental Research and Public Health, 14(1): 68.

22. San Antonio Breast Cancer Symposium Abstracts, newsletters, and other reports of the meeting. Archived 16 May 2010 at the Wayback Machine.
23. Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thürlimann B, Senn HJ (August 2009). "Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009". *Annals of Oncology, 20(8): 1319–29.*
24. "What's new in breast cancer research and treatment?". Cancer. Retrieved 17 November 2015.
25. "Fenretinide (4-HPR): A Preventive Chance for Women at Genetic and Familial Risk?". hindawi. Retrieved 17 November 2015.
26. Edward H. Romond, Edith A. Perez, John Bryant. Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer. The new england journal of medicine. N Engl J Med, 2005; 353: 1673-1684.
27. Brian D. Lehmann, Joshua A. Bauer, Xi Chen, Melinda E. Sanders, A. Bapsi Chakravarthy, Yu Shyr, and Jennifer A. Pietenpol. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest, 2011; 121(7): 2750-2767.
28. Cornelia Liedtke, Chafika Mazouni, Kenneth R. Hess, Fabrice André, Attila Tordai, Jaime A. Mejia, W. Fraser Symmans, Ana M. Gonzalez-Angulo, Bryan Hennessy, Marjorie Green, Massimo Cristofanilli, Gabriel N. Hortobagyi, Lajos Pusztai. Response to Neoadjuvant Therapy and Long-Term Survival in Patients With Triple-Negative Breast Cancer. Journal of clinical oncology. 2008, J Clin Oncol, 26: 1275-1281.
29. William D. Foulkes., Ian E. Smith, and Jorge S. Reis-Filho, M.D. Triple-Negative Breast Cancer. N Engl J Med, 2010; 363: 1938-1948.
30. Katrina R. Bauer, Monica Brown, Rosemary D. Cress, Carol A. Parise, Vincent Caggiano, Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype. Cancer, 2007; 109: 1721–8.
31. Bernard Fisher, Carol Redmond, Nikolay V. Dimitrov, David Bowman, Sandra Legault-Poisson, Lawrence Wigkerham, Norman Wolmark, Edwin R. Fisher, Richard Margolese, Carl Sutherland, Andrew Glass, Roger Foster, and Richard Caplan. A Randomized Clinical Trial Evaluating Sequential Methotrexate and Fluorouracil in the Treatment of Patients with Node-Negative Breast Cancer Who Have Estrogen-Receptor-Negative Tumors.N Engl J Med, 1989; 320: 473-478.
32. Deborah Schrag, Laura D. Cramer, Peter B. Bach, Colin B. Begg. Age and Adjuvant Chemotherapy Use After Surgery for Stage III Colon Cancer. J Natl Cancer Inst., 2001; 93(11): 850-857.
33. Bernard Fisher, Joseph Costantino, Carol Redmond, Roger Poisson, David Bowman, Jean Couture, Nikolay V. Dimitrov, Norman Wolmark, D. Lawrence Wickerham, Edwin R. Fisher, M.D., Richard Margolese, Andre Robidoux, Henry Shibata, Jose Terz, A.H.G. Paterson, Merrill I. Feldman, William Farrar, James Evans, H. Lavina Lickley, Mary Ketner, R.N. A Randomized Clinical Trial Evaluating Tamoxifen in the Treatment of Patients with Node-Negative Breast Cancer Who Have Estrogen-Receptor–Positive Tumors.N Engl J Med, 1989; 320: 479-484.
34. G. Bocci, M. Tuccori, U. Emmenegger, V. Liguori, A. Falcone, M. Del Tacca. Cyclophosphamide-methotrexate ‘metronomic’ chemotherapy for the palliative treatment of metastatic breast cancer.A comparative pharmacoeconomic evaluation. Ann Oncol, 2005; 16(8): 1243-1252.
35. E Claire Dees, Seamus O'reilly, Steven N. Goodman, Susan Sartorius, Marshall A. Levine, Richard J. Jones, Louise B. Grochow, Ross C. Donehower & John H. Fetting. A Prospective Pharmacologic Evaluation of Age-Related Toxicity of Adjuvant Chemotherapy in Women with Breast Cancer. Journal Cancer Investigation, 2000; Volume 18, 6: 521-529.
36. GEORGE P. CANELLOS, VINCENT T. DeVITA, G. LENNARD GOLD, BRUCE A. CHABNER, PHILIP S. SCHEIN, ROBERT C. YOUNG. Combination Chemotherapy for Advanced Breast Cancer: Response and Effect on Survival. Ann Intern Med., *1976; 84(4): 389-392.*