Research Article

Effects of Chemotherapy in Breast Cancer Patients

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Abstract: Introduction: A descriptive, non-interventional study was conducted from April 2011 to September 2013, at KIRAN hospital, Karachi among n = 811 female breast cancer patients to assess the effects of chemotherapeutic agents that were employed for the treatment of breast cancer. The assessment was done so as to see the variation in response of the patients towards the drugs used specifically the adverse effects that have to be combated during therapy.

Methodology: During 3-6 months, a follow up was done to collect data for ADEs (Adverse Drug Events) that occurred among patients after therapy. The SPSS version 16.0 was used for statistical analysis of the data. The adverse events that occurred due to adjuvant chemotherapy including severity, preventability and causality were evaluated using three International scales *i.e.* Modified Schumock and Thornton scale, modified Hartwig's and Siegal's scale and Naranjo's algorithm.

Results and Discussion: Majority of the patients received 6 cycles of FAC therapy (5-fluorouracil, Adriamycin/doxorubicin, cyclophosphamide) and showed good response. The assessment of ADRs using different scales revealed hair loss, nausea, vomiting, anemia and neutropenia as the non-preventable definite effects that were experienced by the patients. Mild to moderate diarrhea/constipation was probably preventable and hence doubtful. Moderately probable effects included mucositis and mouth ulcers whereas possible effects included fever and chills.

Conclusion: Through the right use of medicines, the mild effect of headache and pain could be certainly preventable. Hence chemotherapeutic agents must be chosen for each patient on individual basis to prevent or lessen the toxic effects rendered to them and be useful in the disease course.

Keywords: Adverse drug reactions, Breast cancer, Chemotherapy.
doi.org/10.21089/njhs.22.0067

INTRODUCTION

In Asian women, breast carcinoma is much prevalent and is risk growing with time [1]. It is a multifaceted, complex disease than its incidence [2, 3].

After Israel, the occurrence of breast carcinoma is highest in Asian countries more specifically in Pakistan *i.e.* 2.5 times more as compared to neighboring countries, causing approximately 35% of cancers in women [4]. The information about breast cancer etiology in Pakistan epidemiology is lacking and requires research about its vulnerability aspects in the inhabitants for preventing or treating and reducing its pervasiveness. Due to the variety of elements related to cultural, environmental, reproductive, genetic, lifestyle, geographical regions and ethnic diversity, there is variation in the occurrence of breast cancer. All these factors point out the massive attention to investigate and do research involving people belonging to different population and ethnical background. [4-7].

Management of breast cancer includes identification, classification and organized screening of breast carcinoma [8]. Risk-benefit ratio is considered during selection of treatment *i.e.* the treatment should have more benefit than risk to the life of patient [9]. Breast carcinoma treatment includes different treatment modalities *i.e.* chemotherapy, adjuvant endocrine therapy and local treatment including radiation and surgery [10]. Due to their non-selectivity for cancer and normal cells, anti-cancer therapy causes adverse drug reactions along with their beneficial effects [11].

The quality of life of patient has considerable impact when cancer is diagnosed and he/she undergoes treatment procedure. Distress is elevated and compliance is depressed in breast cancer patients, due to the adverse drug reactions of chemotherapy employed. Therefore, indications in standard guidelines must be in line with pre and post medications. Through research it has been established that local therapy with adjuvant radiation improved local control and overall

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survival in breast cancer patients, hence, decreasing 70% relapse rate proportionally and 9% to 12% proportional decrease in death rates [12, 13]. Unluckily there are no specific standard guidelines in regard to management and anticipation of adverse effects of radiation therapy. The adverse effects that are common in breast carcinoma patients are on skin, hence use of topical agents are suggested for their management [14-16]. This finding is in line with the results of radiation therapy provided to female cancer patients in Karachi, Pakistan [17].

In females with post-menopausal symptoms ,third generation aromatase inhibitors (AIs) *i.e. /* exemestane, anastrozole and letrozoleare are mainly used in substitution to Tamoxifen because of their greater effectiveness particularly in Estrogen receptor –positive breast carcinoma [18].

Some adverse effects like nyalgia, anthralgia and hot flashes are associated with adjuvant hormonal therapy [19, 20]. These findings are similar to the results of a study recently conducted in Karachi, Pakistan in breast cancer patients [48].

For the treatment of breast cancer different types of cytotoxic agents are used that targets cell cycle processes at various steps. The following (Fig. **1**) shows the functioning of cytotoxic agents in patients suffering from cancer [21].

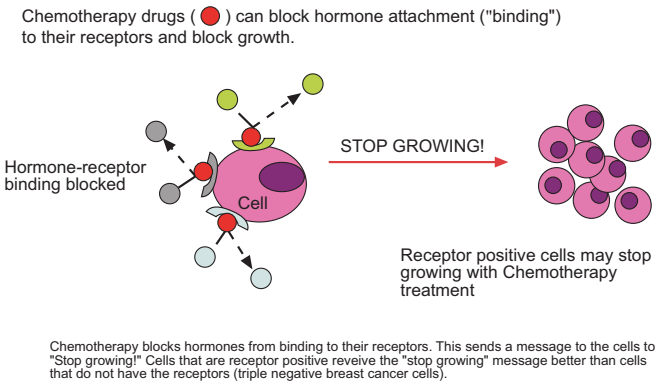

Fig. (1). Functioning of chemotherapeutic agents.

In table **1** some toxicities are listed due to use of different chemotherapeutic agents [22, 23].

Table **1**. Toxicities due to some chemotherapeutic agents used for breast cancer treatment.

Chemotherapeutic Agent	**Toxicities**
Doxorubicin, epirubicin	Myelosuppression, cardiomyopathy, Alopecia, nausea, vomiting, stomatitis, ulceration, necrosis
Paclitaxel	Neutropenia, peripheral neuropathy, Alopecia, fluid retention, myalgia, skin reactions, ulceration, necrosis, stomatitis, hypersensitivity reactions, nausea, vomiting, arrythmia
Cyclophosphamide	Myelosuppression, hemorrhagic cystitis, Alopecia, stomatitis, amenorrhea, nausea, vomiting
Capecitabine	Diarrhea, hand-foot syndrome, Myelosuppression, nausea, vomiting, stomatitis
Gemcitabine	Myelosuppression, Nausea, vomiting, diarrhea, fever, chills, arthralgia, myalgia
Fluorouracil	Myelosuppression, Diarrhea, alopecia, nausea, stomatitis, neurotoxicity
Cisplatin	Myelosuppression, Delayed nausea, vomiting, alopecia, nephrotoxicity, ototoxicity
Carboplatin	Myelosuppression, Nephrotoxicity, alopecia, ototoxicity, neuropathy, nausea, vomiting

METHODOLOGY

This research was a descriptive, non-interventional study in which total n = 811 adult breast cancer female patients with the mean age of 47.02 ± 11.79 years were recruited from KIRAN hospital, Karachi, Pakistan using random convenience sampling. Prior approval was taken from the hospital administration committee to conduct this observational study and positive consent of the patients for their participation in the study was taking using in-person interview and by questionnaire directed by researcher. Data was collected from April 2011 to September 2013 from breast cancer patients. To record the adverse drug events of chemotherapy, treatment data was collected from the patients within 3 to 6 weeks. SPSS (16.0 version) was used for statistical analysis of data. Percentage and frequency were assessed, computed, and classified for any adverse effects that resulted from adjuvant cytotoxic therapy.

Moreover, three International scales namely, modified Schumock and Thornton, modified Hartwig's and Siegel scale and Naranjo's algorithm were used to evaluate severity, causality and preventability.

Inclusion and Exclusion Criteria

Only those participants were recruited who were willing to continue with the study and were cases of breast carcinoma that were being treated at KIRAN hospital, Karachi. It was required for ease of follow-up of the cases. Breast cancer cases were confirmed for having disease and those cases were excluded who had evidence of any cancer other than breast cancer.

RESULTS

Among 811 female breast cancer patients included in this study, majority had stage I or stage II breast cancer. Most of the patients were seen to have significantly good response

after receiving 6 cycles of chemotherapy when they were treated with various cycles and types of chemotherapy (Table **2** and **3**). Mostly FAC therapy (5-fluorouracil, Adriamycin/doxorubicin, cyclophosphamide) was employed for treating the patients (Table **3**). Following chemotherapy, vomiting/nausea (n = 799, 98.52%), alopecia (n = 763, 94.08%), anemia /neutropenia (n = 764, 94.20%), fatigue/anorexia (n = 743, 91.61%) and mucositis/mouth ulcers (n = 743, 91.61%) were the adverse effects most commonly observed in the patients. The assessment of the ADRs using different assessment scales namely, Schumock and Thornton 1992, Hartwig *et al.*, 1992 and Naranjo *et al.*, 1981 for causality, preventability and severity respectively are shown in Table **4**.

Table **2**. Chemotherapy Cycles and response in different age groups of breast cancer cases.

Chemotherapy		**Chemotherapy Response**		
Age group (years)	**No. of cycles**	**Good**	**Partial**	**Total (%)**
20-30 (p=<0.001)	4	5	1	5
	6	52	3	55
	8	2	0	2
	--	--	--	62 (8.15)
31-40 (p=>0.05)	4	5	0	5
	6	175	5	180
	8	11	0	11
	--	--	--	196 (25.78)
41-50 (p=<0.001)	4	7	2	9
	6	244	5	249
	8	3	0	3
	--	--	--	261 (34.34)
51-60 (p=>0.05)	4	4	0	4
	6	91	0	91
	8	2	0	2
	--	--	--	97 (12.7)
>60 (p=>0.05)	4	4	0	4
	6	133	6	139
	8	1	0	1
	--	--	--	144 (18.94)
760 (100)				

Table **3**. Various chemotherapeutic agents used in breast cancer patients.

Chemotherapy Used							
Age group (years)	**Chemotherapy Cycles**	**Capecitabine**	**FAC**	**TAC**	**AC x T**	**5-FU/Vinorelbine or Carboplatin/ Gemcitabine**	**Total (%)**
20-30	4	--	5	--	--	--	5
	6	--	47	4	--	5	56
	8	--	2	6	--	--	8
	--	--	54	10	--	5	69
31-40	4	1	6	--	--	--	7
	6	1	181	5	2	6	195
	8	--	11	--	--	--	11
	--	2	198	5	2	6	213
41-50	4	--	10	1	--	--	11
	6	3	247	4	7	5	266
	8	--	3	--	--	--	3
	--	3	260	5	7	5	280
51-60	4	--	3	--	--	--	3
	6	--	96	--	3	3	102
	8	--	2	--	--	--	2
	--	--	101	--	3	3	107
>60	4	--	3	--	--	--	3
	6	--	132	1	3	2	138
	8	--	1	--	--	--	1
	--	--	136	1	3	2	142
Total		5	749	21	15	21	811

Table **4**. Different scales used for assessment of ADRs due to chemotherapy for breast cancer.

S. No	**ADRs**	**Naranjo's Algorithm**				**Hartwig's and Siegel Scale**			**Schumock and Thornton Scale**		
		DE	**PR**	**PO**	**DO**	**MI**	**MO**	**SE**	**DP**	**PP**	**NP**
1	Anemia/Neutropenia	764	20	--	--	--	--	764	--	--	√
2	Vomiting/nausea	779	20	--	--	--	779	--	√	--	--
3	Diarrhea/constipation	--	35	--	764	743	35	--	--	√	--

4	Alopecia	763	36	--	--	21	763	--	--	--	√
5	Skin/nail discoloration	--	15	42	742	36	--	--	--	--	√
6	Fatigue/anorexia	56	--	743	--	742	36	--	--	--	√
7	Mucositis/mouth ulcers	15	743	21	--	--	758	--	--	√	--
8	Fever/chills	--	56	722	--	742	36	--	--	√	--
9	Headache/pain	--	21	36	742	21	--	--	√	--	--
10	Anxiety	--	--	41	--	41	--	--	√	--	--
11	Other toxicities	15	21	742	--	20	36	--	--	√	--

Where:

DE = definite, PR= probable, PO = possible, DO= doubtful

MI = mild, MO= moderate, SE = severe

DP = definitely preventable, PR = probably preventable, NP = not preventable

The assessment of ADRs using different scales revealed hair loss, nausea, vomiting, anemia and neutropenia among the non-preventable definite effects that were experienced by the cancer patients. Nail and skin discoloration were not preventable but doubtful. Constipation and diarrhea were probably preventable and hence doubtful whereas moderately probable effects included mucositis and mouth ulcers and possible effects included fever and chills. Through the right use of medicines, the mild effect of headache and pain could be certainly preventable [24].

Due to chemotherapy that causes myleosupression, there was occurrence of dose-limited febrile neutropenia [25, 26]. In the females with breast carcinoma, the major damaging chemotherapeutic effect observed in this study was alopecia [27].

In this study it was observed and found that in high risk patients, receiving AC X T therapy, peripheral neuropathy, arthralgia, myalgia and leucopenia were considerably higher than in those to whom FAC therapy was given, but in the latter treatment, diarrhea, hyperpigmentation, anemia and stomatitis were significantly elevated [28].

DISCUSSIONS

Breast carcinoma has been considered as the most common cancer in women worldwide and has contributed to nearly one quarter of all kinds of female cancers [29]. From the developed regions, reports of higher incidence but reduced mortality rates have been seen because of breast carcinoma, although generally forty-five percent of victims and fifty-five percent of deaths are observed in the establishing regions. Some Pakistani studies have gradually discovered breast carcinoma to be the most common cancer in women [30-33]. The cancer patients living in developing countries are found to have inadequate means for combating this disease [34].

In this study, the mean age of breast cancer patients was found as 47.02 ± 11.79 years and other studies that conducted in Pakistan also reported the similar age group for breast cancer patients [35, 36].

The management of breast cancer is achieved through various techniques like radiation, surgery, chemotherapy and endocrine therapy [37]. In this study majority patients of breast carcinoma, *i.e.* n = 776(95.68%) experienced surgery as breast conservation therapy. In this study, systematic management and/or adjuvant radiation were applied to patients after surgical healing. In existing method, also, care standard for stage one to three breast carcinoma is surgery, which is followed by systematic management or adjuvant radiation or combination of both if necessary [38]. Patients (n = 709, 87.42%) received radiation therapy either for 18 or 21 days resulting in 'good' *i.e.* complete responses significantly in more than 90% cases [39].

Hormonal therapy is considered as the fundamental fragment of the breast carcinoma management in complete stages [40, 41]. Adjuvant endocrine therapy *i.e.* Tamoxifen (20 mg) and Letrozole (2.5 mg) was suggested to patients of breast carcinoma (n = 508, 62.63%); Tamoxifen was suggested to most of the patients (96.06%) due to both its agonist and antagonist properties for estrogens [42]. The common feedback observed during the follow ups for adjuvant endocrine therapy among the breast cancer patients of this study was 'good' (complete).

Women having early breast cancer usually have to take systemic adjuvant chemotherapy which is bound for entire

node-positive breast carcinomas and tumors of more than 1cm size [43]. Chemotherapy is principally specified within 3 weeks of surgery and to get greatest outcomes; dose intensity and dose density should be carefully measured. The dosage for general management should be curtailed once adverse effects are observed in the patient [26]. In this research, breast carcinoma patients were given 4 to 8 cycles of adjuvant chemotherapy and most of the patients were in the age group of 41 to 50 years (Table **2**, **3**). The treatment response was examined after administering three cycles of chemotherapy. The feedback 'good' was taken as 'complete response' with omission of closely all biologic or radiologic defects seen at identification time of disease and non-existence of some unique ones; though the patients might suffer from some expected adverse effects. The feedback of 4 to 8 cycles of adjuvant chemotherapy among 20 to 30 years and 41 to 50 years was seen as significantly complete ($p<.001$) (Table **2**).

For management of breast carcinoma, the initial chemotherapy comprised of FAC therapy, then TAC or AC x T therapy (6 cycles) according to the protocol of hospital. Few patients of metastasis were suggested for 8 cycles of Vinorelbine/5-FU or 6 cycles of Gemcitabine. In 2014, 3,485 OPD prescriptions of chemotherapy were assessed by Ketkaew and co investigators and informed that the mostly recommended combinations of chemotherapy were CMF regimen (16.15%, 563 prescriptions), Paclitaxel (12.63%, 440 prescriptions), FAC regimen (36.15%, 1,260 prescriptions), Docetaxel (4.88%, 170 prescriptions) and Capecitabine (7.49% 261 prescriptions). These results are much in line with the results of our study [44]. Kadakia and coworkers [44] observed in their recent study that the utilization of Anthracycline-based Paclitaxel regimen was found more frequently in more than 75% of breast cancer cases; AC followed by paclitaxel was seen to be the frequently used adjuvant therapy in females with early breast carcinoma [45]. It is obvious that approximately fifty to sixty percent breast cancer patients reacted to preliminary chemotherapies such as taxanes, anthracyclines, capecitabine, navelbine, cisplatin, gemcitabine, methotrexate and cyclophosphamide. Anthracyclines and taxanes stand as the most dynamic categories of that drugs are established as first line therapy [46].

In cancer patients, the hereditary polymorphism of enzymes are accountable for signaling paths and biotransformation of drug due to which adverse effects happen upon administration of chemotherapeutic agents [47]. This is also recognized that the chemotherapeutic agents are not selective for just cancer cells and they influence cell lines conveying higher growth and imitation rates. In this study, pre and post therapies were recommended to carcinoma patients for treatment because of chemotherapy induced adverse drug reactions. The methods of management suggested to patients were alike the treatments which is also evident from another study conducted previously in female cancer patients in Pakistan [48].

Adjuvant chemotherapy is usually well tolerated but many adverse effects are observed which include menstruation cessation (which may return or not), along with fatigue and alopecia. Most frequent adverse effects seen in patients because of adjuvant chemotherapy (Table **4**) were Anemia/Neutropenia (n = 764, 94.20%), Alopecia (n = 763, 94.08%), Fatigue/anorexia (n = 743, 91.61%) and Vomiting/ nausea (n = 799, 98.52%).

In the study it was observed that in high risk patients, receiving AC X T therapy, peripheral neuropathy, arthralgia, myalgia and leucopenia were considerably high than the given FAC therapy to the rest of the patients but in the latter treatment, diarrhea, hyperpigmentation, anemia and stomatitis were significantly elevated [48].

An ADR is a response to a drug which is harmful and not deliberate occurring at normal doses when used for prophylaxis, identification, or treatment of disease, or for the alteration of biological function in humans. Universally, in treatment practices potential difficulties are overcome by a mechanism that is set by numerous countries universally by recording ADRs and these databases provide facts and figures about these difficulties. It is required that appropriate standardized scales should be used to measure ADR's precisely. Different scales available for assessing adverse drug reactions that occur by the use of different therapeutic drugs are WHO Assessment Scale, Naranjo's Assessment Scale, Hartwig and Siegel Scale, Modified Schumock and Thornton scale, etc which had been used in this study [49-51] (Table **4**).

CONCLUSION

Breast cancer is a multi faceted disease that has emerged globally but has variations in associated risk factors from region to region. A specific standardized management plan for a recognized breast cancer patient using predictive aspects and prognostics could not be developed but for every patient personalized therapy should be tailored in order to prevent such patients from the noxious effects of medication. ADR databases should be nationally developed that may affect the treatment practices and hence bring about improvements not only in healthcare system but also for the affected patients.

CONFLICT OF INTEREST

Declared none.

ACKNOWLEDGEMENT

The support provided from KIRAN Hospital in this research is highly appreciated, and we are thankful to Dr. Akhtar Ahmed (Director of KIRAN Hospital) in particular.

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Received: March 17, 2017 Revised: March 31, 2017 Accepted: April 03, 2017