

Carcinoma of Breast: Role of Hormone Therapy Pre-Menopausal Women According to Receptors Status in Adjuvant Setting

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ABSTRACT

Aim: Role of hormone therapy in pre-menopausal according to the receptors status with chemotherapy.

Methods: This interventional study was conducted at Department of Pathology Shaikh Zayed Hospital, Lahore from January 2010 to January 2013. Fifty patients of breast cancers of females were included. All females of reproductive age, pre-menopausal with malignancy diagnosed by histopathology were included. The females of post-menopausal, benign breast lesion and carcinoma in situ were excluded. All patients were first FNAC then mastectomy followed by chemotherapy FAC 6-8 cycles and AC 4 + taxol 4. The hormone therapy timoxyfen 20 mg OD were started according to the receptor status. After completion of treatment follow-up visits of patients were planned after every 3 months for 2 years and every 6 months for 3 years.

Results: The mean±SD between the age was 37.86±3.71 years. Fourteen patients have positive lymph node involvement and all cases of ductal cell carcinoma. There were 39 patients of ER, 19 patients of PR and 29 patients of HER2/neu status of positive cases. 32 patients were treated by FAC 6 cycles and 18 patients were treated by AC 4 + Taxol 4.

Conclusion: Neoadjuvant chemotherapy is a well tolerated mode of treatment and leads to good local and systemic control of the disease.

Keywords: Carcinoma, Hormone therapy, Receptor status

INTRODUCTION

Breast cancer risk is increased with age and family history. It is the most common carcinoma in women and accounts for 22% of all female cancers, which is more than twice the prevalence of cancer in women at any other site^{1,2}. Prognosis and management of breast cancer are influenced by the classic variables such as histologic type and grade, tumour size, lymph node status, status of hormonal receptors-estrogen receptor (ER) and progesterone receptor (PR) of the tumour, and, more recently, HER-2 status³. The histopathological examination of the breast cancer bases on the morphological features but more specific prognostic information about its biology are obtained from the immunohistochemical (IHC) testing of the human epidermal growth factor receptor Her2/neu, estrogen receptors and progesterone receptors. Breast cancer is a heterogeneous disease encompassing a number of phenotypically diverse tumours. Expression levels of the estrogen, progesterone and HER2/neu receptors which characterize clinically distinct breast tumours have been shown to change during disease progression and in response to systemic therapies^{4,5}.

HER-2/neu, also known as c-erbB-2 (HER-2), a protooncogene located on chromosome 17, is

amplified and/or the protein (HER-2) over expressed associated with a worse clinical outcome^{6,7}. In contrast, ER is expressed in 70% to 95% of invasive lobular carcinomas and in 70% to 80% of invasive ductal carcinomas, and PR is expressed in 60% to 70% of invasive breast carcinomas^{8,9}. Expression of ER and/or PR generally is associated with a better outcome. Survival and response to hormone therapy are most favorable among women with tumours positive for both ER and PR, intermediate for tumours discordant on receptor status, and least favorable for tumors negative for both^{10,11}. The interrelationship of ER, PR, and HER-2 has come to have an important role in the management of breast cancer. It has been shown that patients with breast carcinoma overexpressing HER-2 do not respond to tamoxifen therapy. Although HER-2 expression generally is inversely correlated with ER and PR expression, the precise extent of its inverse relationship and its association with classic histologic prognostic indicators has not been studied systematically in a large series of cases^{12,13}.

Her-2/neu is over expressed in 20-30% of breast cancer patients; is associated with a more aggressive disease, a poor clinical prognosis and with the targeted therapy agent trastuzumab (Herceptin). Expression of the ER/PR is the most reliable factor for predicting responsiveness to hormonal therapy. The hormone receptor expression measured IHC is accepted as standard evaluation method all over the

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world, but the cut off point in immunohistochemical evaluation is still controversial. Another controversy in testing ER/PR is a mode of presentation of the receptors quantitation as: positive vs negative results or the quantitative results, or both modes. Various scoring systems have been used in IHC evaluation of the ER/PR^{14,15}. Several factors might be responsible for the Her- 2/neu and ER/PR IHC scoring results: the quality assessment system, heterogeneous distribution of positive cells and staining intensity, lack of uniformity in the manual testing, the mode of quantitation - subjective manual vs automated computerised reading, and insufficient training of the observers. Automated microscopy and computerised processing have provided increased accuracy in quantification and standardization. Use of automation in IHC interpretation has decreased the number of ambiguous cases and helped reducing the need for further testing by another modality^{16,17}. The development of the digital pathology and telepathology has increased the interest in implementation of the automated computerized methods in the routine diagnostics.^{18,19}

The expression of specific genes such as the estrogen receptors (ERs), progesterone receptors (PRs) and HER2/neu are indicative of outcome in breast cancer patients, and the clinically relevant sub-groupings are based broadly on ER/PR/HER2/neu status. The ability to classify breast cancers in this manner has obvious beneficial implications for the development of targeted therapies; multigene prognostic and predictive tests have been developed, have been commercialized and have become established as tools in breast cancer diagnostics, although as yet there is little knowledge regarding the precise regulation of these genes and receptors²⁰.

PATIENTS AND METHODS

This interventional study was conducted at Department of Pathology Shaikh Zayed Hospital, Lahore from January 2010 to January 2013. Fifty patients of breast cancers of females were included. All females of reproductive age, pre-menopausal with malignancy diagnosed by histopathology, trucut biopsy, lumpectomy and mastectomy were included. The females of post-menopausal, benign breast lesion and carcinoma in situ were excluded. All patients were first FNAC then mastectomy followed by chemotherapy FAC 6-8 cycles and AC 4 + taxol 4. The hormone therapy timoxyfen 20 mg OD were started according to the receptor status. After completion of treatment follow-up visits of patients

were planned after every 3 months for 2 years and every 6 months for 3 years. X-ray chest and ultrasound abdomen were done every 3 months and bone scan at 6 months interval. Data was entered and cleaned using SPSS 15. Frequency tables were generated for all possible variables. Percentages were calculated for categorical variables. Mean and other parameters of central tendency were calculated for continuous data.

RESULTS

The selected patients were in the age range of 31-45 years. The first age group patients aged 31-35 years 11(22%), in second age group patients aged 36-40 years 29(58%) and in the third age group patients aged 41-45 years 10(20%). The mean±SD between the ages was 37.86±3.71 years (Table 1). There were 30 (60%) of needle core biopsy, 15(30%) of trucut biopsy and 5(10%) of lumpectomy specimens (Table 2). There were 35 cases (70%) of left side of breast and 15 cases (30%) of right side of breast (Table 3). There were 14 patients (28%) have positive lymph node involvement and 36 patients (72%) have negative lymph node involvement (Table 4). Figure 1 showed the ER, PR and HER2/neu status in pre-menopausal women. There were 39 patients (78%) of ER, 19 patients (38%) of PR and 29 patients (58%) of HER2/neu status of positive cases. There were 32 patients (72%) were treated by FAC 6 cycles and 18 patients (36%) were treated by AC 4 + Taxol 4 (Fig. 2).

Table 1: Frequency of patients according to age

Age (years)	Frequency	%age
31 – 35	11	22.0
36 – 40	29	58.0
41 – 45	10	20.0

Table 2: Frequency of patients according to type of specimen (n=50)

Type of specimen	Frequency	%age
Lumpectomy	5	10.0
Trucut biopsy	15	30.0
Needle core biopsy	30	60.0

Table 3: Frequency of patients according to side of breast (n=50)

Side of breast	Frequency	%age
Left	35	70.0
Right	15	30.0

Table 5: Frequency of patients according to lymph node involvement (n = 50)

Lymph node involvement	Frequency	%age
Positive	14	28.0
Negative	36	72.0

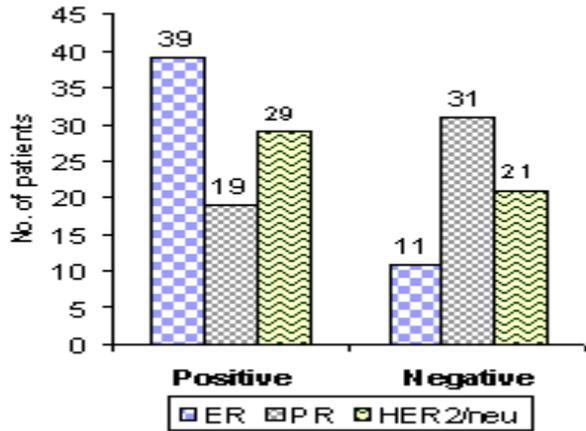


Fig.1: Frequency of +ve and -ve cases according to ER, PR and HER2-neu

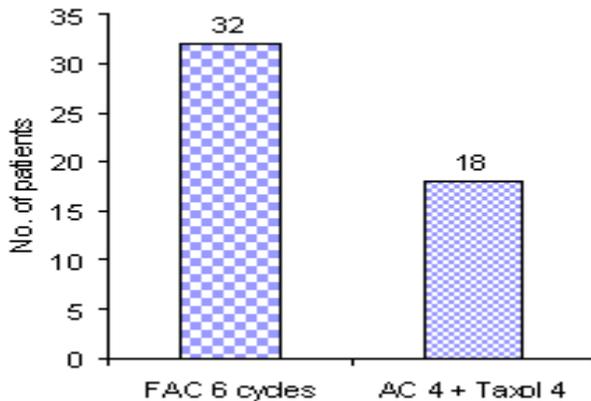


Fig.2: Distribution of patients according to chemotherapy

DISCUSSION

In 1986, tamoxifen was the first drug of its kind approved as monotherapy for the treatment of early breast cancer in node-positive, postmenopausal women. Over the course of almost 20 years, this indication has broadened²¹. The Nolvadex Adjuvant Trial Organisation (NATO) conducted one of the earliest trials identifying tamoxifen’s benefit in delaying recurrence. Patients were randomized to tamoxifen 10mg twice daily for 2 years. The mean follow-up was 21 months. In a subgroup analysis, there was no difference comparing nodal status, menopausal status, or ER positivity between groups. This was the first of many trials conducted to evaluate the effectiveness of tamoxifen in early breast cancer²².

The role of hormonal therapy has evolved over the course of 100 years. Once it was identified that estrogen played an important role in breast cancer, new therapies were created to inhibit its production and function. The gold standard for the past two decades has been the use of tamoxifen in hormone-sensitive patients (estrogen receptor (ER) positive

and/or progesterone receptor (PR) positive). Tamoxifen has been the mainstay of hormonal therapy for many years in early breast cancer. It has proven to be effective but it does have a number of side effects. With the creation of aromatase inhibitors, patients now have another option with better tolerability²³. As the study is retrospective so sufficient information could not be obtained due to limitation of non-availability of patient’s data. However maximum information extracted from files. Regarding the receptor status, following information is obtained. Eleven patients were ER+, 39 patients were ER-, 19 patients were PR+, 31 patients were PR-, and 29 patients were HER2/neu+ and 21 patients were HER2/neu -. This data does not match with the data of Fisher²⁴. But in our set up it is low. The reason may be geographic and racial differences. Chemotherapy related toxicities included grade 2 neutropenia in 7 patients. None of them had febrile neutropenia. Radiation therapy was generally very well tolerated. Temporary skin pigmentation was observed in all patients, which resolved in 2-3 months.

Premenopausal women with hormone receptor–positive breast cancer should receive tamoxifen as an integral part of their therapy. Chemotherapy also has a role and ovarian suppression might have a role, but tamoxifen is a key element of their treatment. Increasingly, we are considering ovarian suppression in addition to tamoxifen in certain patients. Reviewing the variety of data that has been presented today there is a strong argument that ovarian suppression can be an important component of treatment, perhaps even as important as chemotherapy. In women who have very high-risk tumours, multiple positive nodes, large tumours and who do not go into menopause with chemotherapy, particularly younger women less than age 40, I frequently will consider adding ovarian suppression with the caveat that we do not know precisely how much this is going to contribute to their care *and* the caveat that this will undoubtedly increase their likely symptomatology.

CONCLUSION

We conclude that chemotherapy alone is not a sufficient systemic treatment strategy in young patients with hormone receptor-positive breast cancer. Hormone responsiveness is the key for tailoring therapy for young patients with breast cancer. Premenopausal patients with ER-positive tumors represent a distinct population for which tailored treatment is needed. Endocrine therapy is mandatory in this population.

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