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## ORIGINAL ARTICLE

# Factors Influencing Neoadjuvant Chemotherapy Response in Breast Cancer

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## ABSTRACT

**Background:** Breast cancer is a major public health issue globally leading to more than a million deaths annually worldwide. For carcinoma of breast, factors as age of the patient, menopausal status, tumor size, tumor type, tumor grade, estrogen receptor status (ER), progesterone receptor status (PR) and HER2neu expression are important prognostic indicators.

**Objective:** Objective of this study was to observe the response of neoadjuvant chemotherapy on breast tumor and lymph nodes and to identify the clinical and pathological factors.

**Patients and Methods:** This was a descriptive case series conducted in Pathology department, Shaukat Khanum Memorial Cancer Hospital and Research Center Lahore for eight months. Total 55 patients with biopsy proven breast cancer were taken. Data regarding tumor size, tumor type, tumor grade, hormone receptor status (ER status, PR status) and others including age of the patient, menstrual status and HER2neu status was collected on proforma. Lumpectomy and mastectomy specimens of these patients after they have received neoadjuvant chemotherapy were taken. Data were entered and analyzed on SPSS version 10.

**Results:** There were 41 (74.5%) premenopausal and 14 (25.5%) postmenopausal women in our study. Invasive ductal carcinoma was the primary breast tumor in 50 (90.9%) patients while invasive lobular carcinoma was in 5 (9.1%) patients. HER-2/neu showed positivity i-e positive 2+ in 11(20%) cases and positive 3+ in 22(40%) cases. HER 2-neu showed negativity i-e negative 12(21.8%) cases and negative 1+ in 10(18.2%) cases. Grade IV (Complete pathological response) was achieved in 12 patients, Grade III (50-99% response) was achieved in 19 patients, Grade II(<50% response) was achieved in 12 patients and Grade I (No response) was seen in 12 patients. Complete pathological response in lymph nodes was achieved in 8(14.5%) cases, partial response in 19(34.5%) and no response in 18(32.7%) cases. There was no evidence of metastasis in 10(18.2%) cases.

**Key words:** Breast cancer, Neoadjuvant chemotherapy, Pathological factors, Clinical factors.

## INTRODUCTION

Breast cancer is a major public health issue globally with over 1 million new cases diagnosed annually, resulting in over 400,000 annual deaths and about 4.4 million women living with the disease<sup>1</sup>. It is the commonest site specific malignancy and is the most common cause of cancer mortality in the women worldwide<sup>1</sup>. According to hospital based data the incidence in female population in Bahawalpur is 13.2%<sup>2</sup>, in Lahore 26.25%<sup>3</sup>, in Multan 37.6%, and in Northern Pakistan 26.6%. Breast cancer is the commonest cancer among female population in Bangladesh<sup>4</sup>.

The prognosis of breast carcinoma is related to large variety of clinical and pathological factors. These include patient's age, menstrual status, tumor size, tumor type, tumor grade, axillary lymph node status, hormonal receptor status (ER,PR) and HER2neu status. Chemotherapy response in breast tumor is poor in women of less than 35 and

greater than 50 years of age<sup>4,5</sup>.

Chemotherapy has shown increased overall survival in both premenopausal and postmenopausal women in literature. Tumors do shrink following prolonged courses of pre-surgical chemotherapy, so the size of tumor at subsequent surgery is likely to differ from initial tumor size. Neoadjuvant chemotherapy has been documented to improve the long-term survival in women with breast cancer. Neoadjuvant chemotherapy has become the standard treatment of locally advanced breast cancer (LABC) and has quickly come to the forefront in the potential management of patients with earlier-stage operable disease. This chemotherapy is specifically being used in the management of patients with large ( $\geq 3$  cm) and locally advanced (T3, T4, or N2) breast cancers. The goal of chemotherapy given in the adjuvant or neoadjuvant setting is to eradicate occult distant metastases to ultimately improve disease-free

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survival. Overall survival is improved in patients who have complete pathological response as compared with patients with partial response, and this proves to be of prognostic benefit.

Tumor size at diagnosis can be assessed clinically by examination or imaging<sup>5</sup>. Despite frequent and reliable use of neoadjuvant chemotherapy, certain facts regarding the mortality of disease have yet not been illustrated. Different types of breast tumors respond differently to the treatment, some showing good prognosis and others showing worse prognosis. Studies have shown that response of chemotherapy is poor in ILC as compared to IDC<sup>6</sup>. Also, the response of neoadjuvant chemotherapy is different in ER, PR positive/ negative and HER2neu positive/ negative breast tumors. Research with chemotherapy and triple-negative breast cancer has shown that pathological complete response is higher in patients with non- triple negative breast cancer. Axillary lymph nodes are the most common site of lymphatic metastasis in breast carcinoma. Lymph node status at diagnosis is assessed by imaging together with FNAC or core biopsy of any suspicious nodes. Primary systemic therapy(PST) changes the node status and the patients with positive lymph node status become negative showing complete pathological response<sup>7</sup>.

Despite the increasing prevalence of breast cancer in Pakistan, not sufficient work has been done so far to explore the treatment and management strategies to cope with it. Hence the aim of present study was to assess the significance of neoadjuvant chemotherapy in patients with breast cancer and to observe and describe the relation of various prognostic clinical and pathological factors with neoadjuvant chemotherapy.

### MATERIALS AND METHOD

**Setting:** The study was conducted in the Pathology, Oncology and Surgical departments of Shaukat Khanum Cancer Hospital Research Center (SKMCH).

**Duration Of Study:** The study duration was for eight months

**Study Design:** Descriptive case series

**Sampling:** Non probability purposive sampling

**Sample Size:** The study was performed on 55 cases.

**Inclusion Criteria:** Patients with biopsy proven primary breast cancer (age range; 20-60yrs),

undergoing neoadjuvant chemotherapy followed by lumpectomy or mastectomy

**Exclusion Criteria:** Male patients with breast cancer were excluded.

**Methodology:** Fifty-five cases of breast carcinoma found suitable by inclusion criteria were included in the study. An informed consent was taken from all of them. The clinical and pathological data including age, menstrual status, tumor size, tumor type, tumor grade, ER status, PR status and HER2neu status was collected from the files available in the hospital.

The lumpectomy and mastectomy specimens of the female patients with breast cancer who had undergone neoadjuvant chemotherapy were received. The specimens were sliced serially. Representative sections from tumor or any fibrotic area were taken and axillary lymph nodes were isolated. These representative sections were fixed in 10% buffered formalin. Paraffin blocks prepared and H&E slides (Hematoxylin and eosin slides) were examined under the microscope. The response of neoadjuvant chemotherapy on breast tumor was assessed microscopically and were graded as Grade 1 (no response), Grade 2 (<50% response), Grade 3 (50% to 90% response), Grade 4 (complete response with no viable tumor). Response of neoadjuvant chemotherapy on lymph nodes was also assessed microscopically and graded as no response, partial response and complete response; no viable tumor present. H&E slides of trucut biopsies of female patients and slides of hormone receptors ER, PR and HER2 neu that were performed on these trucut biopsies were also taken. Histopathology of original tumor was seen. Then the H&E slides of lumpectomy and mastectomy specimens of the same patients who had undergone chemotherapy were taken. The response of neoadjuvant chemotherapy on breast tumor and lymph nodes was assessed and graded. Information was collected on a proforma regarding patient's name, age, menstrual status, medical record numbers, clinical tumor size (T1,T2, T3), tumor type (invasive ductal carcinoma / invasive lobular carcinoma), tumor grade (I, II, III) , ER status (positive / negative) , PR status ( positive / negative ) and HER2 neu status ( negative, negative 1+, positive 2+, positive 3+ ). The results of response of neoadjuvant chemotherapy on primary breast tumor and lymph nodes were recorded on proforma. Later on a master data sheet was developed and all the information was entered on SPSS.

**Statistical Analysis:** Results of response of neoadjuvant chemotherapy on primary breast tumor and lymph nodes and the clinical and pathological factors influencing the response of neoadjuvant chemotherapy in breast tumor and lymph nodes were obtained. The data was entered in SPSS version 10 and was analyzed accordingly. Data regarding patient's age was stratified. Frequency and percentage was calculated for qualitative variables including tumor size, tumor type, tumor grade, ER, PR, her2neu status, response of neoadjuvant chemotherapy in breast tumor and in lymph nodes.

## RESULTS

55 cases were included in this study. Age of patients ranged from 20 years to 60 years. There were 41(74.5%) premenopausal and 14 (25.5%) postmenopausal women. Invasive ductal carcinoma was the primary breast tumor in 50 (90.9%) patients while invasive lobular carcinoma was primary breast tumor in 5 (9.1%) patients. Regarding tumor size, pathological T stage T1 was present in 7(12.7%), T2 in 31(56.4%) and T3 in 17(30.9%) patients. Tumor grade was found to be of grade I in 1 (1.8%) patient, grade II in 22(40%)

and grade III in 32 (58.2%) patients. ER was positive in 25(45.5%) cases and negative in 30 (54.5%) cases. PR was positive in 20 (36.4%) cases and negative in 35 (63.6%) cases. HER-2/neu showed positivity i-e positive 2+ in 11 (20%) cases and positive 3+ in 22 (40%) cases. HER 2-neu showed negativity i-e negative in 12 (21.8%) cases and negative 1+ in 10 (18.2%) cases. **(Table:1)**

The mastectomy/ lumpectomy specimens of 55 female patients with breast cancer who have received neoadjuvant chemotherapy were taken. Grade IV (Complete pathological response) was achieved in 12 patients, Grade III (50-99% response) was achieved in 19 patients, Grade II (<50% response) was achieved in 12 patients and Grade I (No response) was seen in 12 patients. Chemotherapy response in axillary lymph nodes was also assessed. Complete pathological response was achieved in 8(14.5%) cases, partial response in 19(34.5%) and no response in 18(32.7%) cases. There was no evidence of metastasis in 10(18.2%) cases. 12 patients achieved grade II (<50% response) and 6 patients achieved grade I(no response) **(Table:2)**.

**Table 1:** Comparison of Chemotherapy response in breast tumor in relation to tumor size, tumor type, tumor grade, Estrogen receptor, Progesterone receptor and HER2neu

|                          |                | <sup>1</sup> Chemotherapy response in breast tumor |          |           |          | p-value |
|--------------------------|----------------|--|----------|-----------|----------|---------|
|                          |                | Grade I  | Grade II | Grade III | Grade IV |         |
| <sup>2</sup> Tumor Size  | T1             | 3  | 2        | 2         | 0        | 0.088   |
|                          | T2             | 3  | 5        | 13        | 10       |         |
|                          | T3             | 6  | 5        | 4         | 2        |         |
| <sup>3</sup> Tumor Type  | IDC            | 9  | 11       | 18        | 12       | 0.156   |
|                          | ILC            | 3  | 1        | 1         | 0        |         |
| <sup>4</sup> Tumor Grade | I              | 0  | 0        | 1         | 0        | 0.215   |
|                          | II             | 7  | 5        | 3         | 7        |         |
|                          | III            | 5  | 7        | 15        | 5        |         |
| <sup>5</sup> ER          | Negative       | 6  | 5        | 10        | 9        | 0.398   |
|                          | Positive       | 6  | 7        | 9         | 3        |         |
| <sup>6</sup> PR          | Negative       | 6  | 7        | 12        | 10       | 0.373   |
|                          | Positive       | 6  | 5        | 7         | 2        |         |
| <sup>7</sup> Her2neu     | Negative       | 4  | 2        | 4         | 2        | 0.751   |
|                          | Negative 1+    | 3  | 2        | 2         | 3        |         |
|                          | Positive 2+    | 1  | 3        | 5         | 2        |         |
|                          | Positive 3+    | 4  | 5        | 8         | 5        |         |
| Menstrual status         | Premenopausal  | 10   | 8        | 13        | 10       | 0.627   |
|                          | Postmenopausal | 2  | 4        | 6         | 2        |         |

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1. **Chemotherapy response in breast tumor:**  
Grade I = No response, Grade II = < 50% response, Grade III = 50%-99% response, Grade IV = complete response; no viable tumor
2. **Tumor size:** T1: Tumor more than 1.0 cm but not more than 2.0 cm in greatest dimension, T2: Tumor more than 2.0 cm but not more than 5.0 cm in greatest dimension, T3: Tumor more than 5.0 cm in greatest dimension
3. **Tumor Type:** IDC = Infiltrating ductal carcinoma, ILC = Infiltrating lobular carcinoma
4. **Tumor grade:** Grade I = No response, Grade II = < 50% response, Grade III = 50%-99% response, Grade IV = complete response; no viable tumor
5. **ER** = Estrogen receptor,
6. **PR** = Progesterone receptor
7. **HER2neu** = Human epidermal receptor growth factor

**Table 2:** Chemotherapy Response on Lymph Nodes

|                                    | Frequency | Percent |
|------------------------------------|-----------|---------|
| No Response                        | 18        | 32.7    |
| Partial Response                   | 19        | 34.5    |
| Complete response, no viable tumor | 8         | 14.5    |
| No Metastasis                      | 10        | 18.2    |
| Total                              | 55        | 100.0   |

## DISCUSSION

Neoadjuvant chemotherapy also known as primary or induction chemotherapy is used increasingly in the management of patients with large and locally advanced breast cancer. This treatment is administered with the aim of reducing the size of breast tumor to increase the likelihood of breast conservation and to abolish systemic metastasis in order to improve survival of patients. This therapeutic approach has been evaluated in number of clinical studies, of which the largest study was conducted by the National Surgical Adjuvant Breast and Bowel Project ( NSABP ). It showed that the use of neoadjuvant chemotherapy allowed greater use of breast conservation surgery but the survival of patients was comparable.

Several features are important to evaluate pathological assessment of breast carcinomas to guide the clinician in determining treatment options

and patients prognosis. The aim of this study was to assess the response of neoadjuvant chemotherapy on breast tumor and lymph nodes and to identify clinical/pathological factors which influence the response. These factors included tumor size, tumor type, tumor grade, ER status, PR status and HER2neu. Tumor size has long been recognized as an independent prognostic factor with larger tumors being associated with worse prognosis. A recent study demonstrated that 84% of patients with locally advanced breast cancer experienced a significant reduction in breast tumor size before resection<sup>8</sup>. In a study conducted by National Surgical Adjuvant Breast and Bowel Project trial B-18<sup>9</sup>; 64.7% of T2 tumors and 50% of T3 tumors achieved complete response. It is well established that neoadjuvant chemotherapy can effectively downstage breast tumor in patients with locally advanced breast cancer<sup>10</sup>. In our study, complete pathological response was achieved in 10 (32.2%) of 31(56.3%) T2 tumors and 2 (11.7%) of 17 (30.9%) T3 tumors.

Regarding tumor type, IDC and ILC are the two major types of breast cancer. In our study we assessed the pathological response of chemotherapy in operable invasive lobular carcinoma and invasive ductal carcinoma. The MD Anderson study which was based on 1034 patients including 122 (12%) patients with ILC showed significantly lower pathological complete response (3% versus 15%)<sup>11</sup>. In the IGR study<sup>12</sup> which included 457 patients with T2 > 3cm to T4 tumors treated between 1987 and 1995, 34 (8.3%) cases were ILC. None of them presented with pathological complete response, while it was observed in 9% of overall patients. A multivariate study showed that lobular type is an independent predictor of poor clinical response to chemotherapy. In our study we assessed the pathological response of chemotherapy in operable invasive lobular carcinoma and invasive ductal carcinoma. 55 patients were included, of which there were 50 (90.9%) IDC and 5 (9.1%) ILC. Complete pathological response was achieved in 12 (21.8%) of IDC however none of the ILC patients showed complete pathological response. Our study like other studies showed that neoadjuvant chemotherapy is less effective in invasive lobular carcinoma as compared to invasive ductal carcinoma.<sup>13</sup>

Tumor grade is assessed depending upon architectural and cytological features including

degree of tubule formation, mitotic activity and nuclear pleomorphism. The first description of morphological effects of chemotherapeutic agents dates to 1960 when Waller described nuclear enlargement, cytoplasmic swelling, and nuclear/cytoplasmic vacuolization in a tumor specimen treated with busulphan<sup>14</sup>. Six of fifteen tumors showed a change in overall grade with some tumors showing increase in grade and others showing a decrease. In our study complete pathological response was achieved in 12(21.8%) of total 55 patients. Of these 7 patients have grade II disease and 5 patients have grade III disease. None of patients with grade I disease achieved complete pathological response. This may be due to small sample size because there was only one patient with grade I disease that was included in the study.

Several studies have been conducted with the aim to identify predictive factors of pathological complete response (pCR) after primary chemotherapy (PC). In the International Breast Cancer study group Trial V, there was marked benefit from the use of chemotherapy among postmenopausal patients with hormone receptor negative tumors, whereas postmenopausal and premenopausal patients with hormone receptor positive tumors had no benefit from this treatment<sup>15</sup>. In an trial IX conducted by the same group, the addition of chemotherapy to tamoxifen improved disease free survival in ER, PR negative tumors<sup>16</sup>.

In our study we also observed pCR after primary chemotherapy more in ER, PR negative tumors. Of 55 patients, 9(30%) achieved complete pathological response among 30(54.5%) ER negative patients and only 3(12%) achieved complete pathological response among 25(45.4%) ER positive patients. Regarding response of chemotherapy in PR positive /negative breast tumors, of 55 patients, 10(28.5%) achieved complete pathological response among 35(63.6%) PR negative patients and only 2(10%) achieved complete pathological response among 20(36.3%) PR positive patients.

Limited data is available on the relationship between HER 2 expression and response to chemotherapy. A recently published trial on large number of patients showed a statistically significant positive correlation between HER2 positivity (defined as 3+) and pCR rate<sup>17</sup>. Our data showed that 7(21.2%) of 33(60%) HER2neu positive breast tumors achieved complete pathological response and 5(22.7%) of 22(40%)

HER2neu negative breast tumors showed complete pathological response. However small sample size may be a limitation of these results. Neoadjuvant chemotherapy can clear the axillary lymph node metastasis, as assessed by histological examination. Conversion of clinically involved axilla to pathologically negative status has been reported by both Mc Cready et al<sup>18</sup> and Schwartz et al<sup>19</sup>. Similar findings have been reported in women with less advanced disease at presentation of patients in the neoadjuvant chemotherapy arm of the NSABP B-18 trial who had clinical N1a disease at diagnosis, 71 patients were found to have negative axillary lymph nodes on histological examination after neoadjuvant chemotherapy<sup>20</sup>. In our study pCR was achieved in 8(14.5%) patients and partial response was achieved in 19(34.5%) patients. However there was no response in 18(32.7%) patients and there was no evidence of metastasis in 10(18.2%) patients. Thus neoadjuvant chemotherapy can clear the axilla of microscopic disease before surgery and metastasis are found in 18(32.7%) cases.

## CONCLUSION

Neoadjuvant chemotherapy shrinks tumor size allowing for breast conservation surgery. Response of neoadjuvant chemotherapy is better in IDC as compared to ILC. Response of neoadjuvant chemotherapy is better in grade II tumors, hormone receptor (ER, PR) negative breast cancer and in breast tumors overexpressing HER2neu.

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