Original Article

PATHOLOGICAL COMPLETE RESPONSE OF NEO-ADJUVANT CHEMOTHERAPY (NACT) DOXORUBICIN PLUS CYCLOPHOSPHAMIDE IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER AT JINNAH HOSPITAL LAHORE

Saleha Kanwal, Sara Saeed and Muhammad Akram

**Objective:** To determine the frequency of pathological complete response (pCR) with neo adjuvant doxorubicin and cyclophosphamide in locally advanced breast cancer (LABC).

**Material & Methods:** This prospective study was conducted in 92 patients of locally advanced breast cancer. Pathological response was evaluated on modified radical mastectomy (MRM) samples that was performed after 4 cycles of neo adjuvant doxorubicin and cyclophosphamide.

**Results:** The mean age of the study population was 45.63 years. Among these 38 patients (41.3%) had stage T3 lesion, 53 (57.6%) had T4 and only one patient (1.1%) had T1 at presentation. Ninety patients (97.82%) were with grade 2 and grade 3 tumors. Post anthracycline based NACT 8 (8.7%) patients had pathological complete response, 50 (54.3%) had partial response, 34 (37%) had stable disease. Overall 58 (63%) patients had responded to this treatment.

**Conclusion:** Anthracycline based NACT is a good option for patients with locally advanced breast cancer in developing countries. The results are not comparable with developed countries but better results can be achieved if these patients present at an early stage or taxanes based NACT is used to improve the response.

**Key words:** Breast cancer, Anthracycline based NACT, Pathological complete response

**Introduction**

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females with estimated new cases of 229,060 in United States in 2012. About half of the breast cancer cases and 60% of the deaths are estimated to occur in economically developing countries. Approximately one in every nine of Pakistani women will suffer from breast cancer at some point in their lives. Breast cancer incidence in Pakistan is the highest reported in any South-Central Asian country. It accounts for 38.5% of all female cancers and about half (43.7%) of all breast cancers are locally advanced. In women diagnosed with LABC in Pakistan, patients with lower socioeconomic status (SES) have larger, more aggressive tumors with worsened survival outcomes.

Locally advanced breast cancer (LABC) includes non-metastatic tumours more than 5 cm in size or involving skin/chest wall. It may be associated with fixed axillary lymph nodes, ipsilateral supraclavicular, infra-clavicular or internal mammary nodal involvement. The pCR is defined as absence of the invasive carcinoma on the pathological examination of the breast tissue and axillary lymph nodes. Complete response to chemotherapy is associated with longer disease-free survival (DFS), overall survival and surrogate marker of long term prognosis when compared to non-responders.

The established data shows Clinical Complete Response (CR) in the range of 7 to 65% and pathological CR (pCR) in 4 to 29%. The variation in pathological response is linked with receptors status, grade and tumor characteristics.

**Material & Methods**

It was a descriptive case series, conducted in Department of Oncology, Jinnah Hospital, Lahore. After non probability purposive sampling a total of 92 cases over a period of one year were enrolled. The sample size was calculated with 95% confidence level, 10% margin of error and taking expected percentage of pathologic complete response i.e: 13% of neo-adjuvant chemotherapy with Doxorubicin plus Cyclophosphamide in locally advanced breast cancer. Women between 20-70 years of age with locally advanced breast cancer, who were having no co-morbidities or previous history of treatment were included. They were given 4 cycles of neo adjuvant chemotherapy doxorubicin 60mg/m² and cyclophosphamide 600mg/m² q 3 weekly. MRM with axillary clearance was done 6 weeks after the last cycle of chemotherapy.
Data collected on proforma was entered into the Statistical Package for Social Sciences (SPSS) version 10 software. Quantitative variables like age were presented as mean and standard deviation. Qualitative variables like gender, disease response (complete, partial, or no response) were taken as frequency and percentage.

**Results**

Total 92 patients were enrolled in the study. In 8 resected specimens, no viable residual tumor cells could be identified so the tumor was staged pathologic (p) T0N0 and pathological complete response pCR was concluded as 8.7% (Table 4). The overall pathological response was seen in 58 (63%) patients (complete and partial), while 34 (37%) patients did not respond to treatment.

Patients were categorized as pre and post menopausal groups (age <45yr and ≥45yr).

Out of 49 (53.1%) pre-menopausal women 37 (75.5%) showed response to treatment. There were 43 (46.6%) post-menopausal women, 21 (48.8%) of them had response to therapy. Pre-treatment staging of the tumor showed that 53 (57.6%) patients were having T4 lesion and 48 (52.2%) patients were N2. Out of 8 resected samples with no viable malignant tissue 7 were T4 lesions and 1 was T3 lesion (p=0.05).

Response rates in receptor positive group were significantly higher than receptor negative group (49.9% vs 12.9%  p=0.02). Triple negative patients were 39 (42.3%). 21 (22.7%) of them showed complete /partial pathological response while 18 (19.5%) patient did not show any response.

Majority of the patients enrolled in study were

**Fig-1:** Pathological responses in various tumor sizes.

**Fig-2:** Pathological responses in triple negative breast cancer.

**Fig-3:** Pathological responses in various tumor grades.

**Fig-4:** Pathological responses in receptor positive and negative tumors.
clinically N1,N2. Fifty eight (63%) patients with N1/N2 showed response (complete or partial) (p=0.3) to the treatment. There was only one patient with N0 (Table 1). Most of the patients who responded to treatment were having grade 2 and grade 3 tumor. Eight (8.6%) patients showed pathological complete response to treatment were having grade 2/3 tumor. Fifty (54.3%) patients showed partial response who were with grade 2/3 tumor (Fig. 3).

### Table 1: Response rates according to demographic and baseline tumor characteristics.

<table>
<thead>
<tr>
<th>Response</th>
<th>pCR(^a)</th>
<th>pCR(^b)</th>
<th>PD/SD(^c)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Median)</td>
<td></td>
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<tr>
<td>&lt;45 years (n=49)</td>
<td>3.2% (3)</td>
<td>36.9% (34)</td>
<td>13% (12)</td>
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</tr>
<tr>
<td>≥45 years (n=43)</td>
<td>5.4% (5)</td>
<td>17.3% (16)</td>
<td>23.9% (22)</td>
<td></td>
</tr>
<tr>
<td>Receptor Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receptor status +ve</td>
<td>6.5% (6)</td>
<td>43.4% (40)</td>
<td>19.5% (18)</td>
<td>0.02</td>
</tr>
<tr>
<td>Receptor status -ve</td>
<td>2.1% (2)</td>
<td>10.8% (10)</td>
<td>17.3% (16)</td>
<td></td>
</tr>
<tr>
<td>TND(^*) (n=39)</td>
<td>3.2% (3)</td>
<td>19.5% (18)</td>
<td>19.5% (18)</td>
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</tr>
<tr>
<td>Tumor Size</td>
<td></td>
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<tr>
<td>T3 (n=38)</td>
<td>1.08% (1)</td>
<td>29.3% (27)</td>
<td>10.8% (10)</td>
<td>0.05</td>
</tr>
<tr>
<td>T4 (n=53)</td>
<td>7.6% (7)</td>
<td>25% (23)</td>
<td>25% (23)</td>
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<tr>
<td>Nodal status</td>
<td></td>
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<tr>
<td>N0 (n=1)</td>
<td>0</td>
<td>0</td>
<td>1.08% (1)</td>
<td>0.30</td>
</tr>
<tr>
<td>N1 (n=41)</td>
<td>3.2% (3)</td>
<td>28.2% (26)</td>
<td>44.5% (41)</td>
<td></td>
</tr>
<tr>
<td>N2 (n=48)</td>
<td>5.4% (5)</td>
<td>26% (24)</td>
<td>52% (48)</td>
<td></td>
</tr>
<tr>
<td>N3 (n=2)</td>
<td>0</td>
<td>0</td>
<td>2.1% (2)</td>
<td></td>
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<tr>
<td>Grade</td>
<td></td>
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</tr>
<tr>
<td>G1 (n=2)</td>
<td>0</td>
<td>0</td>
<td>2.1% (2)</td>
<td>0.30</td>
</tr>
<tr>
<td>G2 (n=48)</td>
<td>2.1% (2)</td>
<td>30.4% (28)</td>
<td>19.5% (18)</td>
<td></td>
</tr>
<tr>
<td>G3 (n=42)</td>
<td>6.5% (6)</td>
<td>23.9% (22)</td>
<td>15.2% (14)</td>
<td></td>
</tr>
</tbody>
</table>

A. pCR Pathological Complete Response  B. pPR Pathological Partial Response  C. PD Progressive Disease  D. SD Stable Disease  E. TND Triple Negative Disease

### Discussion

LABC accounts for 40-60% of all breast cancers in developing countries. Pakistan has highest prevalence of breast cancer in Asia especially in young women. 10 years data of local cancer hospital in Karachi showed that 58% patients present with locally advanced breast cancer. In India, between 50% and 70% of patients have locally advanced or metastatic disease at diagnosis. This proportion is high compared with developed countries, where 38% of European and 30% of US breast cancer cases were reported to be either locally advanced at diagnosis or lymph-node positive. 50% of patients with breast cancer in Egypt are reported to be diagnosed with invasive tumors that are larger than 4·5 cm. In USA 40% of invasive breast cancers are diagnosed when tumors are smaller than 1 cm. In current study 53 (57.6%) patients were with T4 and there were 38 (41.3%) with T3 lesion. Clinical and pathological response of breast cancer to NACT is a short-term marker for a long term outcome. LABC is usually inoperable and neo-

adjuvant systemic therapy (NACT) generally is nearly always indicated. The goal of neoadjuvant systemic therapy is to induce tumor response and facilitate local control through surgical resection and radiation therapy. NACT also provides the earliest possible treatment of micro metastases and thus improves survival. Nodal involvement at presentation is associated with a higher risk of locoregional recurrence (HR 1.61, 95% CI 1.28-2.02). In current study there were 41 (44.57%) patients with N1, 48 (52.2%) with N2 and 2 (2.2%) with N3 disease. In contrast to western world where they detect breast cancer early due to screening and better health facilities and in most studies more than 50% patients have no nodal involvement at presentation, this high percentage of nodal involvement in current study indicates the need for screening and early detection. Tumor receptor status (ER, PR) in our patients was more or less similar to the western data available. In current study pCR and pPR was seen in 8.7% and 54.3% patients respectively with AC regimen, but in
studies done in western world the CR and PR rates are 13% (pCR) but 40% (pPR) with the same regimen.13,14 This observation shows that many of our patients responded to treatment in terms of partial response. The reason for high response rates in these studies was that patients were having early stage disease with N0, N1 status. The pathological response is better when taxanes are added into it as NACT. The cPR improves to 26% with taxanes.13 The pCR rate with carboplatin and paclitaxel is up to 31% in patients who were HER2-positive and 67% in ER-negative patients.27 In contrast, in patients with ER-positive, HER2-negative disease, the pCR rate was 12%.14 AC regimen proved effective in this study in terms total pathological response though the cPR was inferior to the published data. For unknown reasons the response rates were high in post menopausal and receptor positive groups. Hormone receptor status seems to be predictive of relative chemoresistance; multiple trials have shown that the probability of achieving a pCR is significantly inferior in tumors expressing hormone receptors.26 The previous available data for response in different receptor groups is controversial.15-17 It is the level of expression of ER and progesterone receptor that might be correlated with the probability of response to neoadjuvant chemotherapy.27 So for any receptor status response to NACT is difficult to comment on. High-grade tumors are more responsive to chemotherapy.18-20 Similar trends were observed in the current study. 63%15 of Grade II & Grade III tumors showed pathological response (complete/ partial) to NACT.

Conclusion
It is concluded from this study that Anthracycline based NACT is good option for patients with locally advanced breast cancer in developing countries. Though the results are not comparable with developed countries, better results can be achieved if these patients present at an early stage. Moreover taxanes can be incorporated in NACT to improve the response. Further research with other available options is also needed. We should focus more on screening and prevention modalities so as to deal with this problem at very first step.

References


