EVALUATION OF PATHOLOGICAL COMPLETE RESPONSE FOLLOWING NEO ADJUVANT CHEMOTHERAPY IN BREAST CANCER PATIENTS

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ABSTRACT

Objectives: To evaluate the rate of pathologic complete response (pCR) in patients with breast carcinoma who received neoadjuvant chemotherapy.

Methodology: The following cross sectional study was conducted at the Department of Oncology, Hayatabad medical complex from December 2022 to May 2023 comprising of 174 patients aged between 30-70 years. Keeping inclusion and exclusion criteria in perspective sampling was done through non-probability consecutive sampling technique. The primary outcome measured was the complete pathological response (pCR), which was assessed based on four categories: stage and lymph node, molecular signature, chemotherapy regimen, and age. Data analysis was achieved using SPSS version 23.0 and results were depicted in the form of description, tables and graphs.

Results: Out of 174 patients, 27 patients achieved a pathologic complete response (pCR). Among the patients classified based on stage and lymph node involvement, the highest number (n= 25, 31.6%) of pCR cases was observed in the stage II lymph node-negative group. The study also analyzed pCR rates based on the molecular signature. The triple-negative subtype exhibited the top pCR rate of 26 %. Furthermore, the study assessed pCR rates based on different chemotherapy regimens. The maximum pCR rate was observed in patients receiving TCHP (20%). Among the patients based on age, those aged less than 35 years had the highest pCR rate (100%).

Conclusion: The propensity of neo-adjuvant chemotherapy (NACT) to convert an in-operable tumor into an operable one is unprecedented. This allows conservative surgery to take place with reduced morbidity and mortality among cancer patients.

Keywords: Neo Adjuvant Chemotherapy; Breast Conservation Surgery; Pathological Complete Response.

INTRODUCTION

Amongst carcinomas afflicting women, breast cancer is at the top and the second leading cause of cancer-related-death in the female gender.[1] Upon its timely diagnosis breast cancer is treatable. Detection in its earliest and most treatable stages is the key to reduce mortality. The chance that a woman might suffer from carcinoma breast at some stage in her life is very high these days, 1 in 9.[2] Invasive breast carcinoma has varying anatomy, clinical presentation and behavior. Upon the basis of molecular signature, breast carcinoma is grouped into luminal A and B, HER-II Enriched and Basal-like.[3] Treatment decisions of breast cancer are based on anatomical and molecular subtypes. Anatomical variables include size of the breast tumor, involvement of the lymph nodes and presence or absence of distant metastasis. Molecular subtypes include assertion of the Estrogen and progesterone receptors and HER-II amplification.[4] Neoadjuvant chemotherapy is treatment given to cancer patients to downstage the disease and make it treatable, rather surgically removable. Early breast cancer is customarily subjected to Neo-Adjuvant-Chemotherapy for remission.[5]

Many trials, including RCTs manifest similar results after Neo-Adjuvant-Chemotherapy or Adjuvant-Chemotherapy. Nevertheless, certain molecular signatures respond better to Neo Adjuvant regimens, causing increased rates of pathologic complete response, which is basically the absence of residual disease on histopathology specimens and regional lymph nodes.[6] Amongst high-risk patients, Neo-Adjuvant-Chemotherapy was presumed to ameliorate the over-all survival. Aims of Neo Adjuvant Chemotherapy are twofold: to make an inoperable disease operable, and to diminish the size of large tumors allowing breast conservation surgery. An added benefit is the lowering of mortal-

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ity in patients whose axillary lymph nodes have been involved by metastatic disease, and allowance of targeted axillary dissection of previously biopsied and clip marked axillary lymph nodes, along with sentinel lymph node dissection in the cases of pathologic complete response.[7] Neo-Adjuvant-Chemotherapy is also acceptable as an in-vivo test for chemo-sensitivity. For a superior disease-free-survival (DFS) and overall-survival (OS), the pathological-complete-response is considered as a surrogate-marker.[8]

The concept of Neo-Adjuvant-Chemotherapy has been used to prepare systemic therapy and improve survival rates. However, it depends upon molecular subtypes of the disease, where Neo-Adjuvant-Chemotherapy can lead to better outcomes with improved survival. This concept proved to be accurate when pathologic-complete-response (PCR) was used as a consequent variable which interacts with the overall-survival (OS).[9] In particular Neo-Adjuvant-Chemotherapy is more efficacious in diseases with a more aggressive molecular subtype such as the triple negative, HER-II positive and high-grade breast carcinoma. On the other hand, Hormone positive, HER-II negative and luminal subtypes respond poorly to Neo-Adjuvant-Chemotherapy.[10,11]

Response to Neo-Adjuvant-Chemotherapy provides prognostic information and guides about adjuvant therapy. As mentioned by the FDA, a pathological-complete-response, is the absence of lingering disease in primary breast tumor, along with the sampled regional-lymph-nodes following completion of Neo-Adjuvant-Chemotherapy. (Yp To / Yp No) PCR correlates with improved survival.[12,13]

Any sign of remaining disease after Neo-Adjuvant-Chemotherapy points towards a heightened risk of recurrence and use for additional treatment.[14] Since Neo-Adjuvant-Chemotherapy allows for considerable deterioration in tumor magnitude, it is imperative to trace the primary tumor site initially at the diagnosis. Before starting upon each individual round of chemotherapy, a physical examination is deemed necessary. Patients with T3, T4 or clinical lymph node involvement are candidates for Neo-Adjuvant-Chemotherapy as upfront surgery may not be possible.

Secondly, it allows initial mastectomy candidates to be able to undergo breast-conserving-surgery. In CALGB 40601(Alliance) study, 43% patients of stage II, III, HER-II positive, who were initially were not aspirants for BCS converted to BCS with Neo-Adjuvant-Chemotherapy.[15] Similarly in BrighTNess trail, 604 patients with stage II, III, TNBC assessed for BCS before and after Neo Adjuvant Chemotherapy of the 141 patients, labelled initially ineligible for BCS, 53.2 % transmuted to BCS after Neo Adjuvant Chemotherapy to carboplatin/velaparib.[16] The following study is being conducted to evaluate the concept of applying neo-adjuvant chemotherapy as a means of making breast cancer more treatable from the surgical point of view.

METHODOLOGY

We piloted a cross-sectional-observation study at the Department of Oncology, Hayatabad Medical Complex commencing from December 2022 to May 2023. The study was based on convenience sampling to assess pathologic complete response in victims with carcinoma breast, who received neo-adjuvant-chemotherapy. Inclusion criteria included female patients diagnosed with early-stage breast carcinoma, who were planned to receive neoadjuvant chemotherapy, age 35 years and above and who were giving consent to be included in the study. Exclusion criteria included patients with metastatic cancer, male patients with carcinoma breast and those patients who did not wish to be part of the study.

Patients who participated in the study underwent a staging workup, completed neoadjuvant chemotherapy according to molecular stages and underwent surgery, which fell into two broad categories, namely breast-conserving/preserving surgery or a proper mastectomy along with sampling of the axilla/ axillary dissection. Histopathological assessment was done for pathologic complete response. Proformas were filled and data was entered into Microsoft excel sheet and transferred to statistical software SPSS version 23.0 for analysis. The results were depicted in the form of description, tables and bar charts.

RESULTS

Among the 174 patients, 79 were classified as stage II, with 32 of them having positive lymph nodes (40.5%) and 47 having negative lymph nodes (59.5%). In the stage II group, 25 patients achieved pCR (31.6%), with 4 patients (16%) in the node-positive group and 21 patients (84%) in the node-negative group. A total of 54 patients (68.4%) did not achieve pCR. The maximum number of pCR cases was observed in the stage II lymph node-negative group (Figure 1). In the stage III group, consisting of 95 patients, 89 patients had positive lymph nodes (93.6%) and 6 patients had negative lymph nodes (6.4%). Only 2 patients (2%) in the stage III group showed pCR, and both of them were node positive. Therefore, pCR was 100% in node-positive stage III patients, while no pCR was observed in node-negative stage III breast cancer patients. Among the stage III patients, 93 patients (98%) did not achieve pCR. Based on the clinical stage and lymph node involvement, the maximum number of pCR cases was achieved in stage II node-positive patients, while only 2% of stage III patients achieved pCR, all of whom were in the node-positive group.

Out of the total patients, 61 patients were classified as luminal A and B subtypes, and

only 4 patients (8%) achieved pCR. Among the 43 triple-negative patients, 11 patients (26%) achieved pCR (Figure 2). For the 37 HER-2 positive patients, 7 patients (19%) showed pCR. Among the 33 triple-positive patients (ER, PR, HER-2 positive), 5 patients (15%) achieved pCR. Thus, the maximum pCR rate based on molecular signature was observed in the triple-negative subtype (25%), followed by HER-2 positive (19%) and triple-positive (15%) subtypes. The luminal A and B subtypes treated with neoadjuvant chemotherapy achieved pCR in only 4% of the patients (Figure 3).

The study analyzed pCR rates based on different chemotherapy regimens. Among the patients receiving AC x4 (anthracycline and cyclophosphamide) followed by Taxane x4, 106 patients (61%) were included, and 15 patients (14%) achieved pCR. For the 17 patients (10%) receiving TCHx06 (docetaxel, carboplatin, trastuzumab), 4 patients (17%) achieved pCR. Among the 46 patients (26%) receiving ACTH (doxorubicin, cyclophosphamide, docetaxel, and trastuzumab), 4 patients (13%) achieved pCR. Lastly, for the 5 patients (3%) who received TCHP (docetaxel, carboplatin, trastuzumab, pertuzumab), 1 patient (20%) achieved pCR. Therefore, the maximum pCR rate was observed in patients receiving TCHP (20%), followed by AC followed by Paclitaxel (14%), TCH (13%), and ACTH (13%). Although the total number of patients achieving pCR was highest in the AC followed by Paclitaxel group (106 patients), the pCR rate was higher in the TCHP group (Figure 4).

The study assessed the pCR rates based on patient age. Among the patients aged less than 35 years, 4 patients (2%) achieved pCR, resulting in a 100% pCR rate. For patients aged 35-50 years (62 patients, 36%), 8 patients (13%) achieved pCR. Among patients aged more than 50 years (108 patients, 62%), 18 patients (17%) achieved pCR. Therefore, the maximum pCR rate was observed in patients aged less than 35 years (100%), followed by patients aged more than 50 years (17%), and patients aged 35-50 years (13%) (Figure 5) .

DISCUSSION

Neo-adjuvant-chemotherapy is the pervasive therapy before embarking upon definitive surgery. Previously, it was used only for inoperable breast carcinomas, with the intent to downstage the tumor to make the tumor operable.[17] Subsequently it has been extended to operable breast carcinomas predominantly to accede breast conservation.

A higher frequency of total or even partial clinical response can be attained with neo-adjuvant-chemotherapy in cases of early breast carcinomas. This results in a greater number of breast conservation surgery all be it with an excessive incidence of local recurrence, but without any consequential rise in long-term recurrence or mortality associated with breast cancer.[18]

A likely elucidation for the inflation in regional reappearance can be attributed to the judicious use of breast-conserving-surgery in patients who are responding positively to NACT. These patients might have had a mastectomy otherwise.[19]

While comparing the two chemotherapy regimens, neo-adjuvant and adjuvant, over all there doesn't seem to be much contrast between survival or breast-cancer-related mortality except for the raised regional re-

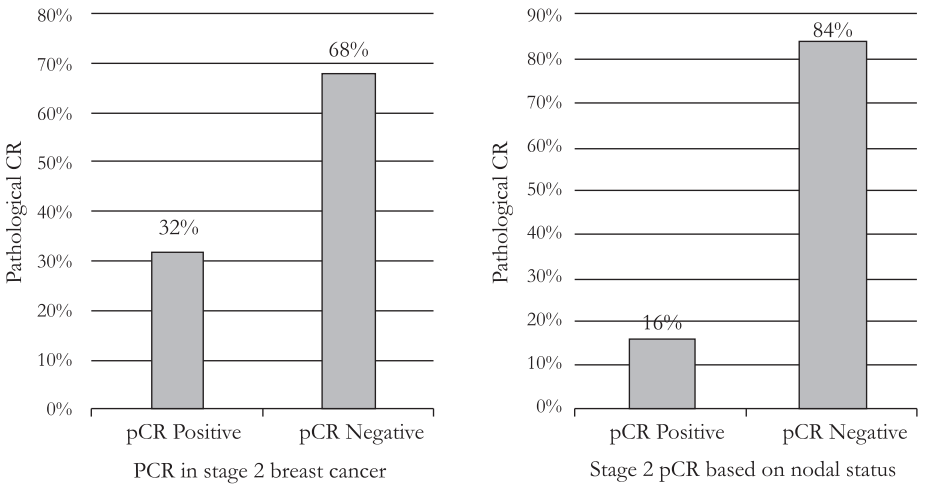

Figure 1: Percentage level of pCR achieved in all patients along with pCR in accordance with nodal status.

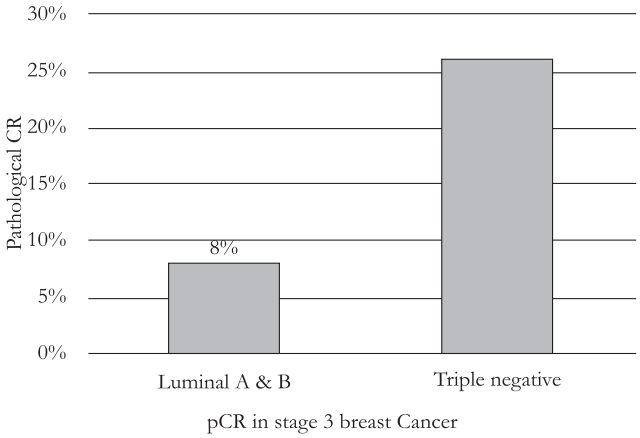

Figure 2: pCR rates in stage 3 Breast cancer both luminal A&B and Triple negative.

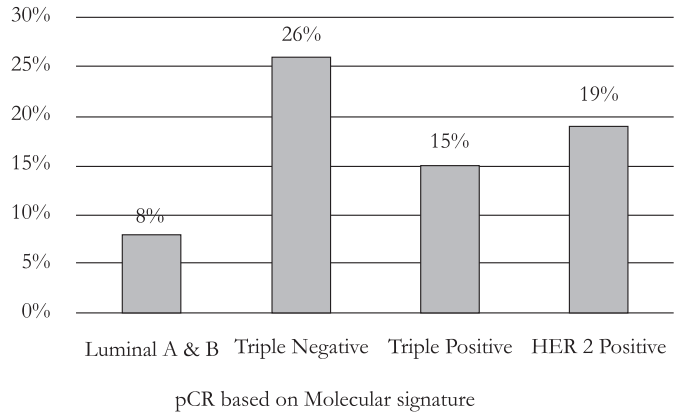

Figure 3: pCR based on molecular signature.

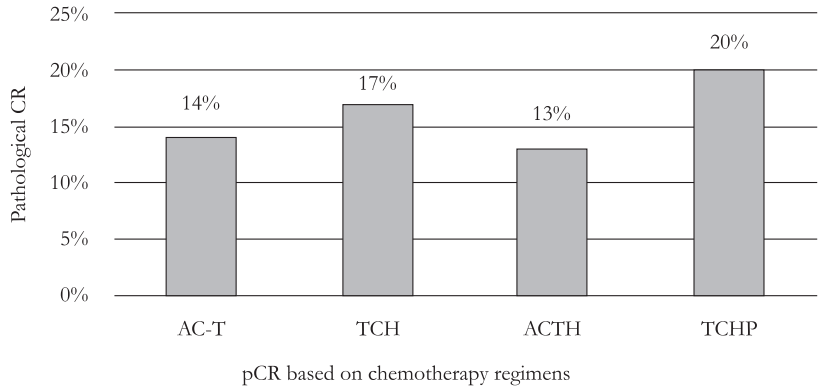

Figure 4: pCR based on chemotherapy regimens

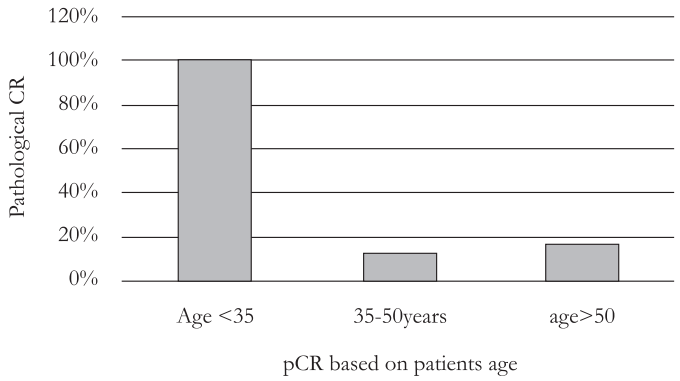

Figure 5: pCR based on patient's age.

appearance of the tumor. Due to this NACT is broadly sanctioned as an in-vivo test for chemo-sensitivity. For a superior overall-survival (OS) and disease-free-survival (DFS), the pathological-complete-response is considered as a surrogate-marker.

As a predictor of diminished long-term recurrence and mortality, the tumor response or better termed pathological complete response is superior than an absent tumor response or residual tumor burden. In literature, outcomes are a cut-above in those patients with a partial-response and are better still in the seldom few who have meagre or a completely absent response to NACT.[19]

Some tumor facets are linked to better outcomes.[20] The surrogate end point, pCR gives a strong premonition for re-occurrence, more so in triple-negative breast carcinomas and HER-II positive breast cancers. So, the pathological-complete-response which is defined as no pathologic tumor in primary breast tissue or lymph nodes is greatest in aggressive subtypes.

In HER-II positive, Hormone negative, treated with NACT + Trastuzumab, pCR achieved was 50.3 %. In TNBC it was 33.6%. In HER-II positive, Hormone negative, treated with NACT, no targeted therapy added, it was 30.2%.

Hence, PCR rates are significantly higher in HER-2 positive, Hormone negative and TNBC compared to Hormone positive and the association was weakest for Hormone positive, HER-2 negative, only 7.5%. Although pCR after neoadjuvant chemotherapy (NACT) is associated with improved disease-free survival (DFS), not all triple-negative breast cancers (TNBCs) and HER2-positive, hormone-negative breast cancers attain pCR.

Moreover, some Hormone positive, HER-2 negative achieve PCR as well. Bio-markers which might be able to hypothesize a therapeutic response to NACT are Ki67 and tumor infiltrating lymphocytes, but these were not utilized in our study.[21,22]

In a study Ki 67 (nuclear protein used as a marker to determine the growth fraction of a given cell population) was significantly associated to prognosis in HR positive, but not in TNBC.[23]

This was a simple cross sectional study determining frequencies and percentages of an outcome variable(pCR). A multicentric study in a cohort or RCT design with a larger sample size could make the findings more convincing. Special statistical tests followed by multivariate analysis and logistic regression would further determine the association between NACT and pCR.

CONCLUSION

At present tines, neoadjuvant chemotherapy has become the mainstay in management of advanced stage breast cancer having favorable outcomes in the post operative period. In order to truly evaluate the effectiveness of NACT in the pathological response to treatment, proper grading of the disease and assessment of sentinel lymph nodes before giving NACT is necessary. According to the results of this study, the frequency of pCR was highest in TNBC and HER-2 positive tumors, but low in hormone positive, HER-2 negative luminal tumors. Among the luminal tumors, only chemo sensitive tumors achieved PCR with NACT.

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Author's Contribution

SC conceived the idea, collected the data and write up of the manuscript. BA performed and contributed in data analysis and write up of the manuscript. RK, SA and AK helped in collection of data and write up of the manuscript. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Authors declared no conflict of interest

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None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.