Clinicopathological Response to Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer and Its Relationship With Molecular Subtypes

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ABSTRACT

Objective To evaluate the changes in the clinicopathological features after neoadjuvant chemotherapy (NACT) in patients with locally advanced breast cancer (LABC) and its relation to molecular subtype characteristics.

Study design Retrospective cross-sectional study.

Place & Duration of study Department of General Surgery, Jinnah Postgraduate Medical Centre (JPMC) Karachi, from November 2024 to April 2025.

Methods The study included 54 female patients between the ages of 18 and 70 years who had stage IIB to IIIC invasive ductal carcinoma based on histological examination. All patients received NACT treatment before undergoing surgical resection. The classification of tumors was done by immunohistochemical analysis of estrogen receptor (ER) and progesterone receptor (PR) combined with HER2/neu expression and Ki-67 measurement. The Miller-Payne grading and Residual Cancer Burden (RCB) was used for measuring pathological results. Statistical data analysis was done through SPSS version 26. Quantitative variables such as tumor size before and after neoadjuvant chemotherapy were compared using the paired t-test. Chi square test was used to find out the association of molecular subtype with the response to NACT. A $p<0.05$ was taken as significant.

Results Majority of the tumors (n=18 - 33.3%) were of a Luminal B subtype. There were 14 (25.9%) HER2-enriched cases. The triple-negative and Luminal A tumors comprised 12 (22.2%) and 10 (18.5%) respectively. Nineteen (35.2%) patients achieved a pathological complete response (pCR) in general with HER2-enriched tumors showing the highest response rate at 50% along-with triple-negative tumors at 41.6%. Molecular subtype noted to have a statistically relevant connection to pCR results ($p=0.041$). The tumors decreased in size from 6.2 cm during pre-NACT to 2.4 cm after NACT treatments ($p<0.001$). Nodal down-staging was noted in 22 (40.7%) patients.

Conclusion All LABC patients showed remarkable clinicopathological outcomes after NACT therapy based on their molecular subtype analysis. HER2-enriched and triple negative breast cancer subtypes achieved better treatment outcomes. Immunochemical tissue analysis improved the treatment outcome.

Key words Breast cancer, Neoadjuvant chemotherapy, Molecular subtypes, Pathological complete response, HER2-enriched, Triple-negative breast cancer.

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INTRODUCTION

Breast cancer in females is the most common malignancy worldwide with public health significance. It is more frequent in low- and middle-income countries.[1] New data from Pakistan's breast cancer registries revealed a rising incidence rates. Most of the patients arrive late for the treatment when the tumor in locally advanced breast cancer (LABC) stage.[2] LABC includes stage III tumors that have various presentations such as tumors greater than 5-centimeters in size and involvement of the skin or chest wall and numerous axillary lymph nodes without distant metastasis.[3] Neoadjuvant chemotherapy stands as the recommended treatment of choice for LABC because it decreases tumor size and increases the chances of breast preservation while identifying how well cells respond to drugs.[4] Clinical findings of pCR after receiving NACT treatment showed better long-term patient survival rates through increased disease-free survival and higher overall survival rates.[5]

The reaction to neoadjuvant chemotherapy differs significantly between different breast cancer patients based upon the molecular characteristics of the tumors.[6] Medical authorities currently divide breast cancer into four intrinsic subtypes; Luminal A, Luminal B, HER2-enriched and triple-negative breast cancer (TNBC) using immunohistochemical (IHC) tests to detect estrogen receptor (ER), progesterone receptor (PR), HER2 status and Ki-67 index information.[7] Treatment strategies depend on the subtypes identification and also predict disease outcomes. Tumors classified as TNBC and HER2-positive tend to achieve higher pCR rates than others.[8,9] Treatment of Luminal A tumors through endocrine-based therapies produces better outcomes compared to chemotherapy since they show reduced sensitivity to chemotherapy.[10]

The data from Pakistan about molecular subtype and their relationships to the clinicopathological effects after NACT remains scarce. The local population data on bio-demographic characteristics needs immediate attention because it supports better patient risk evaluation and improved treatment results.[11,12] This research was conducted to find out the clinical and pathological outcomes after NACT treatment in LABC patients and document their molecular subtype characteristics.

METHODS:

Study design, place and duration:

This was a retrospective cross-sectional study conducted in the Department of General Surgery, Jinnah Postgraduate Medical Centre Karachi, from November 2024 to April 2025.

Ethical considerations: Institutional Review Board of Jinnah Postgraduate Medical Centre granted approval (F2-81/2025-GENL/368/ JPMC) for data analysis. Confidentiality of the data was maintained.

Inclusion and exclusion criteria: The medical records of female patients who underwent treatment for locally advanced breast cancer (LABC) at stage IIB to IIIC based on the American Joint Committee on Cancer (AJCC) staging system between the ages of 18 to 70 years were retrieved. These patients had invasive ductal carcinoma of the breast and received a complete schedule of neoadjuvant chemotherapy and surgical treatment. The study excluded patients who had distant metastases or received prior chemotherapy and radiotherapy. Patients with incomplete medical records and major health conditions affecting treatment results were also excluded.

Sample size estimation: This was a retrospective study, all consecutive patients fulfilling the inclusion criteria during the study period were included. No formal sample size calculation was performed.

Study protocol: Data acquisition were done through a structured proforma. Patients' files together with histopathology reports and treatment documentation records were reviewed. The combination of estrogen receptor and progesterone receptor and HER2/neu status and Ki-67 levels allowed for molecular subtype classification into Luminal A (ER+/PR+, HER2-, low Ki-67) and Luminal B (ER+/PR+, HER2±, high Ki-67) and HER2-enriched (ER-/PR-, HER2+) and triple-negative breast cancer (ER-/PR-, HER2-).

The patients received their treatment according to institutional standards through chemotherapies based on anthracyclines and/or taxanes. The analysis of postoperative pathological response integrated Miller-Payne grading system assessments while RCB classification served as an additional evaluation method.

Statistical analysis: The data were analysed through SPSS version 26. Demographic together with clinical data of patients were presented with the descriptive statistics. Quantitative variables such as tumor size before and after neoadjuvant chemotherapy were compared using the paired t-test, while categorical variables such as molecular subtype and pathological response were analyzed using the Chi-square test. A p-value < 0.05 was considered statistically significant.

RESULTS:

This study included 54 female breast cancer patients who had locally advanced symptoms. The mean age of the patients was 48.7 9.2 year. The Luminal B was the dominant molecular subtype (n=18 - 33.3%). Other types included HER2-enriched (n=14 - 25.9%), triple negative (n=12 - 22.2%) and Luminal A (n=10 - 18.5%). Nineteen (35.2%) patients showed pathological complete response. A total of six (50%) HER2 enriched breast cancers, five (41.6%) of triple-negative breast cancers and six (33.3%) of Luminal B patients achieved pCR while only two (20%) of Luminal A had similar outcome. Details are given in table I. A statistically significant association was observed between molecular subtype and pathological complete response (p=0.041), with higher pCR rates observed in HER2-enriched and triple-negative subtypes (tavke-I). Twenty-five (46.3%) patients had partial benefits from the treatment (table II).

HER2-enriched breast cancers were more frequently had grade 4 and 5 responses among all response grades according to the Miller-Payne grading. An analysis of NACT's impact on tumors showed significant reduction in the size between pre-treatment (6.2 cm) and post-treatment (2.4 cm) measurements with p<0.001. The down staging of affected lymph nodes in the axilla occurred in (n=22 - 40.7%) of cases particularly benefiting patients with HER2-enriched tumors and those with triple-negative breast cancer.

DISCUSSION:

Our findings are consistent with a study of Omair et al where HER2-enriched and triple-negative tumors had the highest pCR rates.[13] Data were comparable as HER2-enriched tumors achieved the highest pCR rate of 50.0% and triple-negative neoadjuvant treatment had a pCR of 41.6%. This showed that non-hormone receptor-positive subtypes respond better to the chemotherapy. The study results validated that molecular subtyping functions as a critical indicator of tissue response to neoadjuvant chemotherapy. Evidence from the study supports subtype-specific treatment planning method. Meta-analysis have shown similar results that NACT increases the rate of breast conservation surgery and is linked to better long term survival.[11]

Tumor size in this study decreased substantially following NACT that was found statistically significant. These findings demonstrate that neoadjuvant chemotherapy successfully downstages tumors which improves the chances of breast-conserving surgery. Molecular subtype assessment predicts the pathological response rates as found in this study. The most notable change was observed in patients with HER2-enriched and triple-negative breast cancers (TNBC).

The published studies support the results of our research as HER2-positive breast cancer along-with triple-negative breast cancer were found more sensitive to chemotherapy than hormone receptor-positive tumors. Among the patients who received anthracycline and taxane-based chemotherapy treatment according to a study the pCR for HER2-enriched and TNBC subtypes success exceeded 45%.[1] Luminal A tumors demonstrated lower pathologic complete response rates to the treatment because they possess a slower cancer progression rate together with reduced sensitivity to chemotherapy drugs than endocrine therapy.[13]

The predictive power of molecular subtyping proves essential for proper patient treatment planning. Immunohistochemical profiling before initiating chemotherapy remains clinically valuable according to our study as statistically significant correlation was found between the molecular subtypes and pathological response. Targeted therapies like trastuzumab and pertuzumab offer optimized treatment responses for HER2-positive cases.[5,14,15]

Limitations of the study: The retrospective nature of the research has drawbacks since the data collected in the files may not provide complete information. The follow-up was also inconsistent. The assessment of pCR was based upon the pathology reports that might show slight differences in the interpretations by different examiners.

Table I: Molecular Subtype and Pathological Complete Response

Molecular Subtype	Number of Patients (n)	pCR Achieved n (%)	p-value
Luminal A	10	2 (20.0 %)	0.041*
Luminal B	18	6 (33.3 %)	
HER2-enriched	14	6 (50.0 %)	
Triple Negative	12	5 (41.6 %)	
Total	54	19 (35.2 %)	

*Statistically significant

Table II: Overall Treatment Response

Molecular Subtype	pComplete Response n (%)	Partial Response n (%)	Minimal/No Response n (%)	p-value
Luminal A	2 (20.0%)	5 (50.0%)	3 (30.0%)	0.27†
Luminal B	6 (33.3%)	8 (44.4%)	4 (22.3%)	
HER2-enriched	6 (50.0%)	5 (35.7%)	3 (14.3%)	
Triple Negative	5 (41.6%)	7 (58.4%)	0 (0%)	
Total	19 (35.2%)	25 (46.3%)	10 (18.5%)	

† Not statistically significant

CONCLUSION:

Molecular tumor subtypes showed substantial relationships with the response to neoadjuvant chemotherapy in breast cancer patients with locally advanced diseases. HER2-enriched and triple-negative breast cancer types showed highest responses. For Luminal A receptor-positive tumors alternative endocrine-based therapies may be considered as treatment options. The standard diagnostic process of medical testing laboratories must incorporate immunohistochemical profiling for developing personalized treatment plans.

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