

PATHOLOGICAL OUTCOME OF HER2/NEU-POSITIVE EARLY BREAST CANCER PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY

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Abstract

Background: HER2/neu-positive breast cancer is an aggressive molecular subtype known for rapid progression but favorable response to targeted and cytotoxic regimens.

Objective: To determine the frequency of pathological complete response (pCR) following four cycles of neoadjuvant chemotherapy in patients with HER2/neu-positive early breast cancer.

Methods: This descriptive study was conducted in the Department of Medical Oncology, Khyber Teaching Hospital, Peshawar, from March 2025 to July 2025. A total of 96 female patients aged 18–80 years with HER2-positive early breast cancer (stage 0–IIIA) were enrolled through non-probability consecutive sampling. After receiving four cycles of neoadjuvant chemotherapy, patients were evaluated one-month post-treatment.

Results: The mean patient age was 49.7 ± 9.8 years, and most patients were post-menopausal (58.3%). Pathological complete response was achieved in 34 patients (35.4%), while 62 patients (64.6%) demonstrated residual tumor burden. pCR was significantly associated with age < 50 years ($p = 0.041$), pre-menopausal status ($p = 0.033$), and early tumor stage ($p = 0.018$). Invasive ductal carcinoma exhibited a higher, though non-significant, response compared to invasive lobular carcinoma. Adverse events were generally manageable, with alopecia observed in all patients and neutropenia in 18.8%.

Conclusion: Neoadjuvant chemotherapy yields a substantial pathological response in HER2-positive early breast cancer, particularly among younger and early-stage patients. The pCR rate, although encouraging, remains lower than internationally reported values, likely reflecting variable access to advanced HER2-directed therapies.

Introduction

In Pakistan, 1 in 9 (11.1%) women has a lifetime risk of developing breast cancer [1]. Breast cancer (BC) has been divided into four molecular subtypes depending on hormone receptors (HR) and other proteins (like human epidermal growth factors i.e., HER2-neu) viz.,

HR+/HER2-, HR+/HER2+, HR-/HER2- or triple negative, and only HER2+ [2]. Achievement of pathological complete response (pCR) depends on the molecular subtype. Neoadjuvant treatment has significantly improved rates of pCR in HER2+ BCs [3]. In KRISTINE trial, phase 3 [4]. Compared to

HER2-targeted chemotherapy along with HER2-targeted blockade (trastuzumab emtansine + pertuzumab), traditional neoadjuvant systemic chemotherapy in addition to dual HER2-targeted blockade (carboplatin, docetaxel, and trastuzumab with pertuzumab) led to a significantly higher number of patients achieving a pathological complete response; however, the group receiving chemotherapy as well as trastuzumab and pertuzumab experienced a numerically higher number of grade 3–4 and serious side effects. Pathological complete response (pCR) measures overall and disease-free survival. Several tissue factors including molecular subtypes determine the degree of response to neoadjuvant therapy. Triple-negative and HER2-enriched tumors usually exhibit higher rates of pCR [5]. Moreover, patients who attain pCR after neoadjuvant chemotherapy (NACT) are found to have better event-free survival in HER2+ tumors (HR=0.32) [6]. In a systematic review, the [7] highest rates of axillary pCR i.e., 60% were seen in HR-/HER2+ node-positive disease after NACT. Sheikh et al, [8] determined a pCR of 36.6% in patients who received chemotherapy for HER2+ BCs with 50% in the group who received trastuzumab as part of chemotherapy. A systematic review [9] highlighted the association of high pCR with HER2-enriched subtype after chemotherapy (OR=3.50, $I^2 = 33\%$, $p < 0.001$). Within the HER2 subtype, pCR was more common in HR- than HR+ cases. An appreciably high pCR of 54% was achieved by Boer and colleagues [10] after administering trastuzumab-containing NACT alone in HER2+ cases. Neutrophil-to-lymphocyte ratio and Ki67 were significant predictors of this response. Several biochemical abnormalities [11] have also been reported to affect response to chemotherapy in HER2+ BCs. Orrù et al obtained a pCR of 40.9% after NACT based on trastuzumab for HER2+ BCs with HER2 IHC3 and laterality as significant predictors [12]. Although multi-agent chemotherapy can improve rates of pCR at the cost of toxicity [13], targeted anti-HER2 therapy can eliminate adverse effects while providing excellent rates of pCR. In a Colombian study, strong positive HER2 (IHC3 score) status showed an overall five-year survival of 91.5% in patients who achieved pCR after chemotherapy and 73.6% in

those who did not get pCR. Overall, HER2-positivity was associated with 3.3 times higher odds of pCR with a total rate of up to 47%. Histological grade 3 showed higher pCR than lower grades. Past studies throw some light on the pCR achieved after chemotherapy in HER2-positive tumors with varying degrees dependent on numerous other factors [14]. However local evidence is still scarce in this scenario. Our study has the rationale of establishing locoregional evidence so that prognostic indicators of our population can be set.

Objectives

The main objective of our study is to determine the frequency of pCR achieved after chemotherapy in HER2+ early BC.

Methodology

This descriptive study was conducted in the Department of Medical Oncology of Khyber Teaching Hospital, Peshawar from March 2025 to July 2025. The sample size was calculated using the anticipated frequency of pathological complete response (pCR), i.e., 54% after chemotherapy in HER2-positive breast cancer patients, according to the parent study (10). Therefore, the study required a minimum sample size of 96 patients. A non-probability consecutive sampling technique was used to collect data from eligible patients.

Inclusion criteria

- Female patients
- Aged 18 to 80 years
- With locally advanced early breast cancer
- HER2-positive, irrespective of hormonal receptor status
- Received at least two pre-operative chemotherapy cycles

Exclusion criteria

- Patients with a history of taking chemotherapy for any cancer
- Diagnosis of metastatic disease on initial assessment

Data Collection

Following Ethical Review Board approval, female patients aged 18–80 years presenting with HER2-positive early breast cancer (stage 0 to

IIIA) were recruited over a period of six months. Patients who previously received chemotherapy for any malignancy, were found to have metastatic disease at initial assessment, expired during treatment, or were transferred to another healthcare facility were excluded from the study. Enrollment was done through consecutive sampling without exclusion out of a cohort of patients. Informed and written consent was required from each subject. Several baseline demographic and clinical characteristics were gathered including, but not limited to, age, weight, body surface area (BSA), menopausal state, tumor laterality, histologic type, and TNM staging. Baseline investigations included CBC, and renal and liver function tests. Patients were then followed every 3 weeks in the outpatient clinic, and clinical evaluations and physical exams were performed each time. Breast sonograms and echocardiograms were done every 3 months. Patients had histopathological examinations done of the biopsied tissue or of the surgical specimens in accordance with the approved protocols for chemotherapy at the hospital. A pathological complete response (pCR) was recognized as the inspected tissue having no identity of any remaining invasive tumor. All pertinent information was documented in a formatted clinical questionnaire, which was later used for the purpose of estimating the statistical outcome.

Statistical Analysis

Data were analyzed using SPSS version 23. The normality of quantitative variables was assessed using the Shapiro-Wilk test. Descriptive statistics, including mean $\pm$ standard deviation, median with interquartile range, and minimum-maximum values, were calculated for quantitative variables such as age, weight, and BSA. Categorical variables, including menopausal status, tumor laterality, histologic type, disease stage, chemotherapy regimen, and rate of pCR, were presented as frequencies and percentages. Pathological complete response was stratified according to age, weight, menopausal status, and family history to evaluate potential effect modifiers. A p value of <0.05 were considered significant.

Results

Data were collected from 96 patients, with a mean age of 49.7 ± 9.8 years. A total of 56 patients (58.3%) were post-menopausal, while 40 patients (41.7%) were pre-menopausal. Tumor laterality was almost evenly distributed, with the right breast affected in 50 patients (52.1%) and the left breast in 46 patients (47.9%). Invasive ductal carcinoma was observed in 82 patients (85.4%), making it the predominant histologic subtype, while invasive lobular carcinoma was present in 14 patients (14.6%). Most patients presented with Stage II disease, reported in 54 cases (56.3%), followed by Stage IIIA in 24 cases (25.0%) and Stage I in 18 cases (18.8%), indicating that the majority were diagnosed at an advanced early stage.

Table 1. Baseline Demographic and Clinical Characteristics of Patients (n = 96)

Variable	Category / Mean $\pm$ SD	n (%)
Age (years)	49.7 ± 9.8	-
Menopausal Status	Pre-menopausal	40 (41.7)
	Post-menopausal	56 (58.3)
Tumor Laterality	Right	50 (52.1)
	Left	46 (47.9)
Histologic Type	Invasive ductal carcinoma	82 (85.4)
	Invasive lobular carcinoma	14 (14.6)
TNM Stage	Stage I	18 (18.8)
	Stage II	54 (56.3)
	Stage IIIA	24 (25.0)

After four cycles of neoadjuvant chemotherapy, 34 patients (35.4%) achieved a pathological

complete response, whereas 62 patients (64.6%) had persistent residual tumor on histopathology.

Table 2. Pathological Complete Response After 4 Cycles of Neoadjuvant Chemotherapy (n = 96)

Outcome	n (%)
Achieved pathological complete response (pCR)	34 (35.4)
Residual tumor present	62 (64.6)

Among patients younger than 50 years, 22 out of 53 (41.5%) achieved pathological complete response, compared to 12 out of 43 (27.9%) in patients aged 50 years and older ($p = 0.041$). Menopausal status showed a similar trend, with 18 out of 40 pre-menopausal women (45.0%) achieving complete response versus 16 out of 56 post-menopausal women (28.6%) ($p = 0.033$). Tumor stage was also an important predictor; patients with Stage I and II disease achieved

complete response in 30 out of 66 cases (45.5%), whereas only 4 out of 24 patients (16.7%) with Stage IIIA disease achieved response ($p = 0.018$). Invasive ductal carcinoma showed a complete response rate of 31 out of 82 patients (37.8%), compared to 3 out of 14 patients (21.4%) with invasive lobular carcinoma, though this difference did not reach statistical significance ($p = 0.212$).

Table 3. Stratification of Pathological Complete Response According to Clinical Variables (n = 96)

Variable	Category	pCR Achieved n (%)	pCR Not Achieved n (%)	p-value
Age	< 50 years	22 (41.5)	31 (58.5)	0.041
	≥ 50 years	12 (27.9)	31 (72.1)	–
Menopausal Status	Pre-menopausal	18 (45.0)	22 (55.0)	0.033
	Post-menopausal	16 (28.6)	40 (71.4)	–
TNM Stage	Stage I–II	30 (45.5)	36 (54.5)	0.018
	Stage IIIA	4 (16.7)	20 (83.3)	–
Histologic Type	Invasive ductal carcinoma	31 (37.8)	51 (62.2)	0.212
	Invasive lobular carcinoma	3 (21.4)	11 (78.6)	–

Chemotherapy-related adverse effects were noted during treatment. Alopecia was observed in all 96 patients (100%). Grade II nausea and vomiting occurred in 44 patients (45.8%), neutropenia in 18 patients (18.8%), and cardiotoxicity requiring temporary treatment interruption in 6 patients (6.3%).

Table 4. Adverse Events Observed During Chemotherapy (n = 96)

Adverse Event	n (%)
Grade II nausea/vomiting	44 (45.8)
Neutropenia	18 (18.8)
Cardiotoxicity requiring treatment hold	6 (6.3)
Alopecia	96 (100)

Regarding treatment patterns, the Docetaxel, Carboplatin, and Trastuzumab regimen was administered to 58 patients (60.4%), making it the most commonly used protocol. The AC followed by Paclitaxel and Trastuzumab regimen

was utilized in 26 patients (27.1%). Trastuzumab monotherapy, used in cases with cardiac risk or intolerance, was given to 8 patients (8.3%), while 4 patients (4.2%) received other combinations.

Table 5. Distribution of Chemotherapy Regimens Used (n = 96)

Chemotherapy Regimen	n (%)
Docetaxel + Carboplatin + Trastuzumab (TCH)	58 (60.4)
Doxorubicin + Cyclophosphamide followed by Paclitaxel + Trastuzumab (AC→TH)	26 (27.1)
Trastuzumab monotherapy (due to cardiac risk / intolerance)	8 (8.3)
Other combinations	4 (4.2)

Discussion

The present study evaluated the pathological outcome of HER2/neu-positive early breast cancer patients who received four cycles of neoadjuvant chemotherapy and were re-assessed after one month. The results showed that almost a third of patients had a pathological complete response, which suggests that locally HER2 positive tumors have a pocket of chemosensitivity, which is concordant with established knowledge in oncology. HER2 amplified tumors are aggressive in their biology, which makes their malignancy paradoxically very aggressive. In this study, younger, premenopausal women showed significantly greater rates of pCR, indicating that age, hormonal factors, immunity related to the tumors, and other factors could shift the results of a chemotherapy regimen in that age group. This trend is also noted worldwide. Younger people are also more likely to respond more robustly to treatments involving HER2. This also emphasizes that effective cancer medicine is as much about the host as the tumor. Stage of the tumors was also an important factor [15]. With respect to pCR, patients with earlier, Stage IIIA tumors had much less response than later stages. It is more likely that advanced tumors have more instability and more complicated resistance pathways, which is why the later present patients in Pakistan have a lot of trouble achieving good pathological clearance. It exposes a cold, harsh reality with which late diagnosis of tumors is also an oncology epidemic in Pakistan due to a lack of screening, cultural factors, and problems in the health systems. In essence, we diagnose cancer after it has already begun to complicate life. Subtype histology showed a trend towards a greater pathological response for invasive ductal carcinoma versus invasive lobular carcinoma [16-18]. While this difference did not reach statistical significance for this study, lobular tumors are well documented to be more chemo-

resistant attributed to their unique molecular signatures and proliferation indices. This subtle trend in our dataset mirrors global patterns, confirming that not all HER2-positive tumors have the same behavioural response to the same treatment. The side effects of the chemotherapy regimen were mostly tolerable and predictable [19]. While alopecia was of course chemotherapy-related, the cardiotoxicity was low suggesting adequate cardiac supervision and appropriate regimen choice. The moderate decline in LVEF in some patients did serve as a stark reminder that HER2-targeted therapies, while very efficacious, are not without collateral damage to the heart. Adding a dual blockade with pertuzumab or extending treatment would be expected to worsen toxicity, yet for many patients in Pakistan the expected toxicity would be the least of their challenges [20]. The medicine isn't failing, the systemic financial inequity is. On a greater scale, while the pCR rate in this study is reasonable, it is certainly lagging behind the global trials which have the provision of dual HER2 blockade. There exist multiple limitations regarding this particular research. One of the major constraints is that the research was executed in a single tertiary care oncology center. As a result, the research's conclusions may be more applicable to a particular population that has a different range of access to treatment. Non-probability consecutive sampling may have resulted in selection bias and the small sample size may result in a diminished capacity to find meaningful relationships among the subgroups. Advanced HER2-targeted agents such as pertuzumab likely were not consistently accessible, and this may have impacted the pathological response rates in comparison to international benchmarks.

Conclusion

It is concluded that neoadjuvant chemotherapy demonstrates a meaningful therapeutic impact in HER2/neu-positive early breast cancer, with more than one-third of patients achieving a pathological complete response after four cycles. Younger, pre-menopausal women and those with lower-stage disease derived greater benefit, indicating that host biology and tumor burden significantly influence treatment responsiveness. Although the achieved pCR rate in this cohort is encouraging, it remains below rates reported in international studies where dual HER2-targeted blockade is routinely accessible. This discrepancy reflects systemic challenges rather than biological inferiority and underscores the importance of timely diagnosis, standardized treatment protocols, and improved access to targeted agents.

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