ORIGINAL ARTICLE

Real-world Outcomes of Neoadjuvant Dual HER2 Blockade with TCHP in Early and Locally Advanced HER2-Enriched Breast Cancer: Experience from a South Indian Tertiary Oncology Center

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Abstract

Background: HER2-enriched breast carcinomas are biologically aggressive but highly responsive to targeted therapy. Data on the real-world effectiveness of neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) from Indian oncology practices remain sparse.

Objectives: To assess pathological complete response (pCR), treatment-related toxicities (CTCAE v5.0), and survival outcomes among patients with nonmetastatic HER2-positive breast cancer receiving neoadjuvant TCHP.

Materials and methods: A bidirectional observational analysis was conducted on 55 patients with HER2-positive nonmetastatic breast carcinoma who were treated at a tertiary oncology center. Patients received neoadjuvant TCHP followed by definitive surgery. Clinical response, radiological response, pCR, treatment compliance, toxicity, disease-free survival (DFS), and overall survival (OS) were evaluated. Statistical associations with pCR were analyzed using Fisher's exact test.

Results: The median age of the patients was 47 years. Stage III disease was the most common (70.9%). Hormone receptor negativity was observed in 56% of the patients. Clinical complete response was achieved in 85% of the patients, whereas radiological complete remission occurred in 58%. A pCR was documented in 60% of the cohort. A significant correlation with pCR was observed for clinical response ($p < 0.001$), radiological response ($p = 0.002$), and uninterrupted treatment completion within 18 weeks ($p = 0.013$). Hormone receptor expression and baseline stage did not significantly influence pCR rates. Diarrhea and neutropenia were the predominant toxicities, whereas clinically relevant cardiotoxicity was not encountered. At a median follow-up of 29 months, the estimated 3-year DFS and OS were 95% and 97.2%, respectively.

Conclusion: Neoadjuvant TCHP demonstrated substantial pathological response rates, acceptable tolerability, and encouraging survival outcomes in HER2-positive breast cancer. Adherence to the planned treatment timeline significantly influenced therapeutic efficacy.

Keywords: Dual HER2 blockade, HER2-amplified breast cancer, Neoadjuvant systemic therapy, Pathological complete response, Pertuzumab, Trastuzumab.

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Introduction

Breast carcinoma remains the leading malignancy affecting women globally and continues to be a major contributor to cancer-related mortality. Approximately one-fifth of breast cancers demonstrate amplification or overexpression of the human epidermal growth factor receptor-2 (HER2), which is associated with increased tumor aggressiveness, rapid disease progression, and poorer clinical outcomes when untreated. The introduction of HER2-targeted agents has markedly improved survival and transformed the therapeutic management of this molecular subtype.

Neoadjuvant systemic therapy has become an integral component in the treatment of early-stage and locally advanced HER2-positive breast cancer. In addition to facilitating surgical downstaging, neoadjuvant therapy offers an opportunity to evaluate *in vivo* tumor sensitivity to treatment. The achievement of pathological complete response (pCR) following neoadjuvant treatment has emerged as an important surrogate marker associated with improved long-term survival outcomes.

The combination of trastuzumab and pertuzumab with taxane- and platinum-based chemotherapy has become a widely accepted neoadjuvant approach for HER2-positive disease. Major clinical trials including NeoSphere, TRYPHAENA, and BERENICE have demonstrated substantial improvements in pCR rates and encouraging survival outcomes with dual HER2 blockade strategies.

Although evidence from international clinical trials is well established, published data describing outcomes in routine Indian oncology practice remain relatively limited. Real-world studies are particularly relevant in resource-constrained settings where treatment delays, financial limitations, and variations in supportive care may influence therapeutic outcomes. The present study was therefore conducted to evaluate pathological response, treatment tolerability, and short-term survival outcomes among patients with nonmetastatic HER2-positive breast cancer treated with neoadjuvant TCHP at a tertiary oncology center in South India.

Materials and Methods

This bidirectional observational study was conducted at the Department of Medical Oncology, ESIC Medical College and Hospital, Hyderabad, Telangana. The study included both retrospective and prospective evaluations of patients with nonmetastatic HER2-positive breast cancer treated with a neoadjuvant TCHP regimen followed by definitive surgery.

Patient Selection

Patients with histopathologically confirmed HER2-positive invasive breast carcinoma who received neoadjuvant systemic therapy with the TCHP regimen were enrolled in the study.

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Inclusion Criteria

- Age ≥18 years.
- Histologically confirmed HER2-positive breast carcinoma.
- Clinical stage I–III disease without distant metastasis.
- HER2 positivity confirmed by immunohistochemistry (IHC 3+) or *in situ* hybridization (ISH) as per the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines.
- Eastern Cooperative Oncology Group (ECOG) performance status 0–2.

Exclusion Criteria

- Presence of metastatic disease at diagnosis.
- Significant uncontrolled cardiac disease or baseline left ventricular dysfunction.
- Patients unfit for systemic chemotherapy.

Treatment Protocol

Patients received neoadjuvant chemotherapy combined with dual HER2-directed therapy using the TCHP regimen at 3-week intervals. A total of six cycles was planned whenever clinically feasible.

The treatment protocol consisted of intravenous docetaxel at a dose of 75 mg/m^2 and carboplatin calculated at an area under the curve (AUC) of 6 on day 1 of each cycle. Trastuzumab was administered with an initial loading dose of 8 mg/kg followed by maintenance doses of 6 mg/kg every 3 weeks. Pertuzumab was delivered as an 840 mg loading dose during the first cycle followed by 420 mg every 3 weeks thereafter.

All patients received standard supportive care measures including corticosteroid premedication, antiemetic prophylaxis, hydration, and hematopoietic support according to institutional practice guidelines. Use of granulocyte colony-stimulating factor support was individualized based on hematological tolerance and clinician assessment. Definitive surgical management was performed after completion of neoadjuvant systemic therapy.

Evaluation of Response

Treatment response was assessed using clinical examination and imaging studies following completion of neoadjuvant therapy. Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging was utilized for radiological evaluation wherever available. Clinical complete response (cCR) and radiological complete response (rCR) were documented based on posttreatment assessment findings.

Resected surgical specimens from both the breast and axillary tissue were examined histopathologically to determine treatment response. pCR was defined as the absence of residual invasive carcinoma in both breast tissue and regional lymph nodes (ypT0/is ypN0).

Statistical Analysis

Continuous variables were summarized using the median and range. Categorical variables were expressed as frequencies and percentages. Associations between clinicopathological parameters and pCR were analyzed using Fisher's exact test. Survival analysis was performed using the Kaplan–Meier estimates.

Results

Clinicopathological Profile

A total of 55 patients with nonmetastatic HER2-positive breast cancer were included in this study. The median age at diagnosis was 47 years (range, 33–67 years). Postmenopausal women constituted the majority of the study population (36/55, 65.5%), and 19 patients (34.5%) were premenopausal. One male patient was included in the study of 55 patients. Hormone receptor-negative tumors were slightly more common and were identified in 31 patients (56.4%), whereas hormone receptor positivity was observed in 24 patients (43.6%).

With respect to primary tumor stage, T2 disease was the most frequent presentation and was noted in 23 patients (41.8%), followed by T4 tumors in 15 (27.3%) and T3 tumors in 13 (23.6%) patients. T1 lesions were identified in four patients (7.3%). Axillary nodal involvement was common, with N2 disease observed in 21 patients (38.2%) and N1 disease in 17 patients (30.9%). N0 and N3 diseases were present in nine (16.4%) and eight patients (14.5%), respectively. All patients had nonmetastatic disease at the time of presentation. According to the American Joint Committee on Cancer (AJCC) 8th edition staging system, stage III disease constituted the largest subgroup and was observed in 39 patients (70.9%), whereas stage II and stage I diseases were present in 14 patients (25.5%) and 2 patients (3.6%), respectively. A total of 52 patients (94.5%) received all six cycles of the TCHP regimen. Treatment interruption with completion of only four cycles occurred in three patients (5.5%) secondary to grade 3 diarrhea. Additionally, 48 patients (87.3%) completed treatment within the intended duration of 18 weeks, whereas treatment delays beyond 18 weeks were documented in seven patients (12.7%).

Therapeutic Response

Response Outcomes

Clinical complete response (cCR) was documented in 47 patients (85%), and radiological complete remission (rCR) was achieved in 32 patients (58%). A pCR was observed in 33 patients (60%), whereas residual invasive disease persisted in 22 patients. Minimal residual disease (<1 mm) was identified in one patient.

Clinical complete response was observed in all patients who achieved pCR (33/33, 100%), whereas only 14 of 22 patients (63.6%) with residual pathological disease showed cCR. This association between clinical response and pCR was statistically significant ($p < 0.001$). Similarly, rCR showed a strong correlation with the pathological eradication of the disease. rCR was documented in 28 of 33 patients (84.8%) who achieved pCR, compared with only 4 of 22 patients (18.2%) with residual pathological disease. This difference was statistically significant ($p = 0.002$).

Hormone receptor co-expression and baseline stage were not significantly associated with pCR achievement. The distribution of hormone receptor status between the pCR and residual disease groups was comparable and did not reach statistical significance ($p > 0.9$). The proportion of patients across clinical stages was similar between the pCR and residual disease groups, and no statistically significant association was observed ($p > 0.9$) (Table 1).

Impact of Treatment Timeliness

Completion of neoadjuvant therapy within the planned 18-week duration was significantly associated with improved pathological response outcomes. Among the 48 patients who completed treatment on schedule, 32 (66.7%) achieved pCR, whereas only one of seven patients (14.3%) with treatment delays beyond 18 weeks attained pCR. Delays in treatment were primarily attributed to drug nonavailability, hematological toxicities, and treatment-related diarrhea, and were associated with a significantly higher incidence of residual pathological disease (85.7% vs 33.3%; $p = 0.013$).

Adverse Events and Treatment Tolerability

Treatment-related toxicities were generally manageable and consistent with the established safety profiles of the TCHP regimen.

Diarrhea represented the most frequently encountered adverse event, affecting

Table 1: Association of clinical variables with pCR

Subgroup variable	*Overall (N = 551)*	*pCR achieved (N = 33)*[1]	*Residual disease (N = 22)*[1]	*p-value*[2]
Clinical response (cCR)				<0.001
cCR achieved	47/55 (85%)	33/33 (100%)	14/22 (64%)	
Clinical residual	8/55 (15%)	0/33 (0%)	8/22 (36%)	
Radiological response (rCR)				0.002
rCR achieved	32/55 (58%)	28/33 (85%)	4/22 (19%)	
Radiological residual	23/55 (42%)	5/33 (15%)	18/22 (81%)	
Hormone receptor status				>0.9
HR positive	24/55 (44%)	15/33 (45%)	9/22 (41%)	
HR negative	31/55 (56%)	18/33 (55%)	13/22 (59%)	
Clinical stage				>0.9
Stage I	2/55 (3.6%)	1/33 (3.0%)	1/22 (4.5%)	
Stage II	14/55 (25%)	8/33 (24%)	6/22 (27%)	
Stage III	39/55 (71%)	24/33 (73%)	15/22 (68%)	
Treatment duration				0.013
18 weeks	48/55 (87%)	32/33 (97%)	16/22 (73%)	
>18 weeks	7/55 (13%)	1/33 (3.0%)	6/22 (27%)	

[1]*n/N* (%); [2]Fisher's exact test

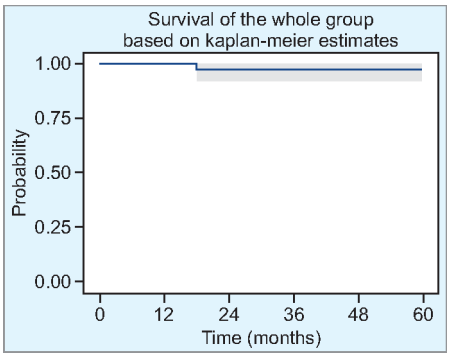

Fig. 1: Kaplan–Meier curve for OS Kaplan–Meier survival curve showing OS among patients treated with neoadjuvant TCHP regimen for nonmetastatic HER2-positive breast cancer. The estimated 3-year OS was 97.2%, with median OS not reached because of the very low number of death events observed during the study period

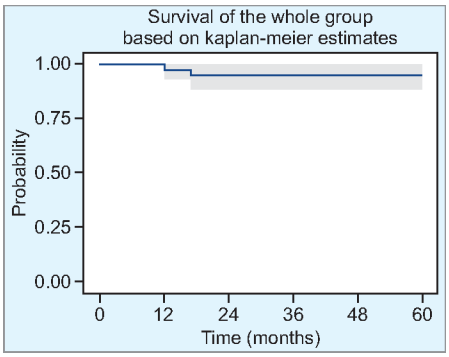

Fig. 2: Kaplan–Meier curve for DFS Kaplan–Meier survival curve showing DFS among patients treated with neoadjuvant TCHP regimen for nonmetastatic HER2-positive breast cancer. The estimated 3-year DFS was 95.0%, with median DFS not reached due to the low number of recurrence events during follow-up

17 patients overall, including grade 3 diarrhea in seven patients. Neutropenia occurred in three patients, with grade 3 neutropenia documented in two cases. One patient experienced grade 2 thrombocytopenia.

Importantly, no patient developed symptomatic cardiac dysfunction or a clinically meaningful decline in the left ventricular ejection fraction during therapy.

Survival Analysis

The median follow-up duration for the study cohort was 29 months (range, 5–60 months). During follow-up, two patients who had initially achieved pCR subsequently developed isolated intracranial recurrence in the form of brain metastases without evidence of extracranial disease; one patient died following recurrence, while the other remained on palliative systemic therapy with ongoing follow-up. The median disease-free survival (DFS) and overall survival (OS) were not reached during the study period because of the low number of recurrence and death events observed. The estimated 3-year DFS and OS rates for the study population were 95.0% and 97.2%, respectively, reflecting favorable short-term survival outcomes with neoadjuvant TCHP therapy (Figs 1 and 2).

Discussion

The current study demonstrates favorable real-world outcomes with neoadjuvant TCHP therapy in patients with HER2-positive nonmetastatic breast cancer treated in a tertiary care oncology setting in India. A pCR rate of 60% was observed in our cohort, which is broadly consistent with findings reported in major international studies evaluating dual HER2 blockade in the neoadjuvant setting. Previous landmark trials including NeoSphere, TRYPHAENA, and BERENICE have documented pCR rates ranging from approximately 45–66% depending on chemotherapy backbone and patient characteristics. Our findings support the reproducibility of these outcomes in routine clinical practice outside highly controlled trial environments.

An important finding from the present analysis was the strong relationship between clinical response, radiological response, and final pathological eradication of disease. Patients who demonstrated complete response on clinical examination and imaging were significantly more likely to achieve pCR after surgery. This observation highlights the practical value of posttreatment response assessment in predicting therapeutic effectiveness and guiding postoperative management decisions. Similar associations between imaging response and pathological outcomes have been reported previously in HER2-positive breast cancer cohorts.

Another clinically relevant observation in this study was the influence of treatment adherence and timely completion of therapy on pathological response. Patients who completed neoadjuvant treatment within the planned treatment duration showed significantly higher pCR rates than those who experienced delays. In our setting, interruptions were largely related to toxicities, supportive care limitations, and occasional issues with drug availability. Such challenges are commonly encountered in real-world oncology practice, particularly in resource-limited healthcare systems. These findings emphasize the importance of uninterrupted delivery of HER2-targeted therapy to maximize treatment efficacy.

Hormone receptor co-expression did not demonstrate a statistically significant effect on pCR rates in our cohort. Although several larger studies have reported comparatively higher pCR rates among hormone receptor-negative tumors, the relatively limited sample size in the present study may have influenced subgroup analysis. Nevertheless, meaningful pathological responses were observed across both hormone receptor-positive and hormone receptor-negative disease categories.

The toxicity profile observed in this study was generally manageable and aligned with previously published safety data for TCHP-based therapy. Gastrointestinal adverse events, particularly diarrhea, represented the most common toxicity, while neutropenia was the predominant hematological complication. Importantly, clinically significant cardiac

toxicity was not observed in our cohort. The absence of major cardiotoxicity further supports the safety profile of anthracycline-sparing HER2-directed regimens described in earlier studies.

During follow-up, two patients experienced isolated central nervous system (CNS) relapse despite initially achieving pCR. HER2-positive breast cancer has a known tendency for brain metastasis, partly related to limited penetration of monoclonal antibody therapies across the blood–brain barrier. This finding suggests that although pCR is associated with favorable outcomes, it does not completely eliminate the risk of disease recurrence, particularly within the CNS.

Short-term survival outcomes in the present study were encouraging, with estimated 3-year DFS and OS rates of 95% and 97.2%, respectively. Because only a small number of relapse and mortality events occurred during follow-up, median survival endpoints were not reached. These findings are consistent with previously published long-term analyses demonstrating improved survival with effective HER2-targeted neoadjuvant therapy.

Real-world evidence from Asian and European populations has similarly demonstrated substantial pathological response rates with dual HER2 blockade in routine oncology practice. Such studies are valuable because real-world patient populations frequently include individuals with advanced-stage disease, comorbidities, and treatment interruptions that are often underrepresented in clinical trials.

The present study contributes important Indian real-world data regarding neoadjuvant TCHP therapy in HER2-positive breast cancer. However, certain limitations should be acknowledged, including the modest sample size, single-center design, and relatively short follow-up duration. Larger prospective multicentric studies with longer surveillance are required to better characterize long-term survival outcomes and recurrence patterns in the Indian population.

Conclusion

This study provides supportive real-world evidence regarding the efficacy and tolerability of neoadjuvant TCHP therapy in patients with HER2-positive nonmetastatic breast cancer treated in a tertiary oncology setting in India. High pCR rates and encouraging short-term survival outcomes were observed with acceptable treatment-related toxicity. Achievement of cCR and rCR showed a strong association with pathological eradication of disease, while delays in treatment delivery adversely affected therapeutic outcomes. These findings reinforce the value of dual HER2 blockade as an effective neoadjuvant strategy and underscore the importance of treatment adherence and supportive care optimization in routine oncology practice. Further large-scale prospective studies with extended follow-up are warranted to validate these observations.

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Ethical Statement

Institutional Ethics Committee approval was obtained prior to the commencement of the study (approval no. IEC-S0401/06/2024).

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Conflict of Interest

The authors declare no conflicts of interest.

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