AHOT | Acta Haematologica Oncologica Turcica

Acta Haematol Oncol Tur

Letter to the Editor

DOI: 10.4274/ahot.galenos.2025.2025-11-3

Therapeutic Response Heterogeneity in the Neoadjuvant Setting: Observations from a Case of HER2-positive, Hormone Receptor-negative Breast Cancer

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Keywords: Breast cancer, human epidermal growth factor receptor 2, targeted therapy, tumor biology, tumor heterogeneity

Dear Editor,

The neoadjuvant treatment period serves as a critical window for evaluating tumor biology and chemosensitivity, particularly in breast carcinomas characterized by well-defined molecular subtypes. Here, we present a case of human epidermal growth factor receptor 2 (HER2)-positive, hormone receptor-negative breast cancer that exhibited differential therapeutic sensitivity, which we interpret in light of current evidence regarding intratumoral heterogeneity.

Case Presentation

A 38-year-old female patient was diagnosed with invasive ductal carcinoma of the breast, stage cT2N2M0 (American Joint Committee on Cancer 8th edition), estrogen receptor- and progesterone receptor- negative, HER2-overexpressing, with a Ki-67 proliferation index of 60%. She received four cycles of neoadjuvant doxorubicin and cyclophosphamide [doxorubicin + cyclophosphamide (AC)] chemotherapy. Contrary to expectations, interim breast magnetic resonance imaging revealed progressive disease. The regimen was subsequently intensified by adding carboplatin to a standard docetaxel-trastuzumab-pertuzumab combination, resulting in four cycles of docetaxel + carboplatin + trastuzumab + pertuzumab (TCHP). A near-complete radiologic response was achieved following this modification (Figure 1). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Inadequate Response to Anthracyclines: Indicative of Underlying Molecular Discordance?

Anthracycline-based chemotherapy remains a cornerstone in the treatment of highly proliferative breast tumors, particularly those overexpressing HER2 [1]. The high Ki-67 index in this case would typically suggest increased chemosensitivity [1]; however, disease progression following AC challenges this assumption. While HER2 positivity and high proliferation indices are generally associated with favorable treatment responses, this case highlights the limitations of relying solely on immunohistochemical markers for therapeutic prediction [2]. Increasing evidence supports the existence of distinct molecular subtypes within HER2-positive disease—such as "HER2-enriched," "luminal B-like," and "basal-like"—each displaying unique response patterns [2].

Implementation of TCHP as a Salvage Strategy in the Neoadjuvant Setting

Given the radiologically documented progression, the treatment regimen was escalated to TCHP. This strategy aimed not only to enhance cytotoxic effects but also to improve anti-HER2

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Received: 10.11.2025 **Accepted:** 30.12.2025 **Epub:** 13.01.2026

Cite this article as: Öztürk G, Tunçbilek N, Topaloğlu S, Kıyıcı B. Therapeutic response heterogeneity in the neoadjuvant setting: observations from a case of HER2-positive, hormone receptor-negative breast cancer. Acta Haematol Oncol Turc.

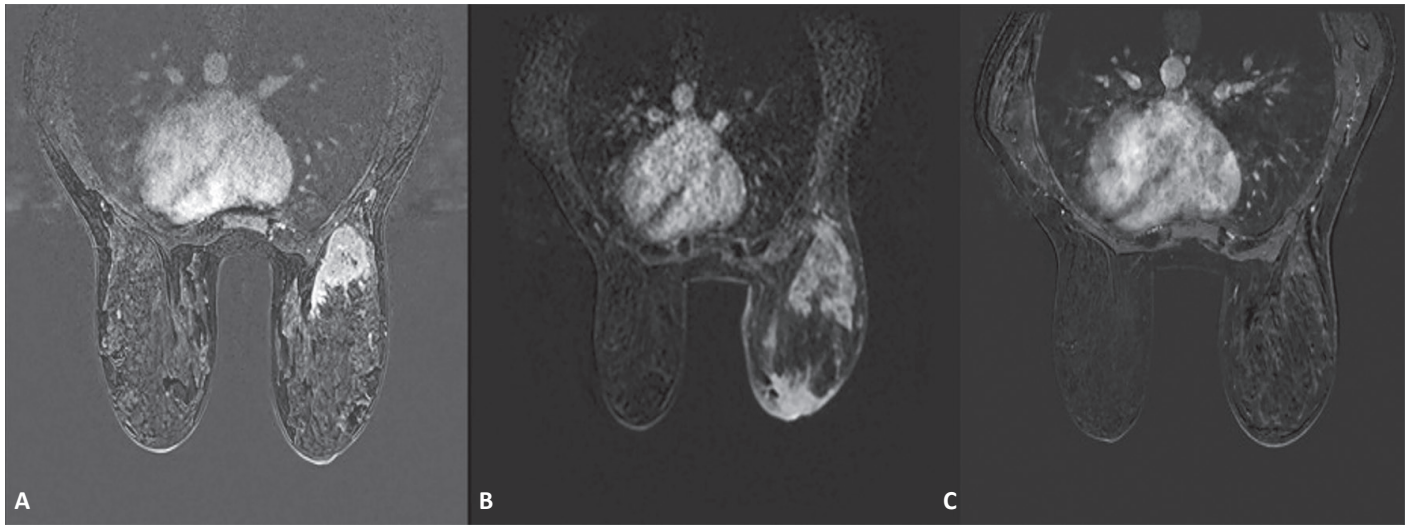

Figure 1. Serial breast MRI images demonstrate the radiological course of a HER2-positive malignant lesion in the right breast. At baseline (A), a malignant mass is observed in the upper outer quadrant of the right breast. At the 3-month follow-up (B), MRI reveals findings consistent with disease progression. Following the addition of anti-HER2 therapy (C), subsequent imaging shows a near-complete radiological response
HER2: Human epidermal growth factor receptor 2, MRI: Magnetic resonance imaging

efficacy through the synergistic interaction with carboplatin, a DNA-damaging agent. The clinical benefit observed aligns with growing evidence supporting the combined use of platinum agents and targeted therapy in biologically aggressive tumors [3]. Furthermore, the substantial increases in pathological complete response (pCR) observed with neoadjuvant trastuzumab highlight that the therapeutic efficacy of HER2-directed treatments can vary markedly depending on the underlying molecular architecture of HER2-driven tumors [4]. The phase III TRAIN-2 trial demonstrated that anthracycline-free, carboplatin-containing regimens achieved pCR rates equivalent to those achieved with anthracycline-based therapy while providing a more favorable toxicity profile, thereby supporting the use of TCHP as a potent but safer alternative in patients with high-risk disease [5]. Similarly, the KRISTINE trial showed significantly higher pCR rates with TCHP than with the antibody-drug conjugate trastuzumab emtansine plus pertuzumab, underscoring the robust early efficacy of taxane- and platinum-based anti-HER2 therapy in tumors with aggressive biology [6]. Taken together, these data highlight TCHP as a highly effective neoadjuvant option that offers strong cytoreduction, an improved safety profile over anthracycline-containing regimens, and the advantage of introducing full anti-HER2 therapy from the outset of treatment.

Divergent Therapeutic Outcomes as a Manifestation of Genomic Complexity

The marked difference between disease progression observed under AC therapy and the near-complete clinical and radiologic response achieved with TCHP reflects distinct therapeutic sensitivities arising from underlying biological diversity. Even among tumors with similar histologic features and receptor expression profiles, considerable genomic heterogeneity may be present, resulting in variable responsiveness to sequential treatment modalities [2]. In this context, TCHP therapy resulted in substantial tumor regression and produced meaningful clinical and radiologic downstaging. Although a pCR was not achieved and postoperative assessment demonstrated ypT1aN2a disease—with micrometastatic involvement in five lymph nodes, the largest metastatic focus measuring 5 mm—the conversion of an initially bulky nodal burden into microscopic disease strongly suggests a favorable biological sensitivity to intensified treatment. Accordingly, the presence of residual disease should not be interpreted as diminishing the therapeutic impact of TCHP, but rather as a complementary pathological finding underscoring the extent to which early progression under AC was effectively reversed through treatment intensification. The magnitude of tumor regression observed with TCHP is further supported by preclinical and clinical evidence demonstrating enhanced activity of platinum-containing anti-HER2 combinations in HER2-positive tumors that are biologically heterogeneous, genomically unstable, or TP53-mutated [7]. Taken together, this case highlights the genomic complexity of HER2-positive disease and emphasizes the crucial influence of timely, biology-guided therapeutic modification on clinical outcomes.

Conclusion

This case illustrates the necessity of reevaluating therapeutic strategies in real time when clinical expectations are not met and reinforces the role of the neoadjuvant period as a biological assay. The observed discrepancy in response, despite favorable prognostic markers, highlights the importance of integrated molecular profiling in clinical decision-making. In carefully selected patients, early therapeutic intensification may yield significant benefits and may represent a key component of personalized oncologic care.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.T., S.T., Concept: G.Ö., S.T., Design: G.Ö., S.T., Data Collection or Processing: N.T., B.K., Analysis or Interpretation: G.Ö., B.K., Writing: G.Ö., N.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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