HER2-low breast cancer: A new clinical entity

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HER2-positive breast cancers (BC) account for ~15-20% of total BC cases with a poor prognosis. The outlook for these patients has improved drastically with the advent of anti-HER2 targetted treatments.[1] According to American Society of Clinical Oncology/College of American Pathologists (ASCO-CAP) 2018 guidelines, HER2 is considered positive when it is overexpressed on immunohistochemical (IHC) assay with a score of 3+ or 2+ with gene amplification on in-situ hybridization (ISH) assay while negative when IHC staining is 0, 1+, or 2+ with no gene amplification on ISH.[2]

This dichotomous classification was recently upended when patients with HER2 2+ unamplified and HER2 1+ tumours were identified as promising targets for new anti-HER2 therapies specifically antibody-drug conjugates (trastuzumab deruxtecan or T-DXd).[3,4] Thus, a new classification term "HER2-low" was introduced for these patients.[3] This was a major leap in treating patients whose disease is chemo-refractive and HER2-driven. However, the emergence of the HER2-low subgroup poses many challenges regarding its pathological classification and biology in early-stage disease.

One of the main concerns in classifying HER2-low tumours is the choice of techniques employed i.e. IHC and ISH. These techniques have only been employed to quantify HER2 overexpression in BC, without distinguishing between low levels and no HER2 expression. This makes it imperative to first develop and validate more sensitive and reliable techniques for classifying HER2-low tumours in clinical settings. Until these new methods are developed, the risk of treating new patients and patients already on anti-HER2 therapies poses a significant challenge to clinicians.

Latest GLOBOCAN statistics highlight the critical need to improve BC management practices in countries like Pakistan, where disease burden is high, with more than 30,000 BC cases reported in 2022 alone.5 We reviewed the total number of patients who attended our Breast Oncology clinics in 2022 and re-analysed their HER2 status following the new classification. Based on the available results of 528 patients, 117 (22%) early-stage BC patients now fit the criteria of the HER2-low subgroup with either HR+ or HR- status. This emphasizes the importance of properly monitoring such patients and investigating their disease biology and response to existing therapies.

It is currently debatable if HER2-low status in BC constitutes a distinct entity in the early stage and whether it has prognostic value. Treatment strategies for individuals with advanced BC have undergone a significant shift because of the introduction of the unique targetable subgroup of HER2-low BC. Nevertheless, several difficulties have surfaced lately along with this significant advancement. Through the creation of more sensitive and repeatable HER2 tests, we will need to optimize techniques for the identification of HER2-low BC. Future developments in the definition of HER2-low might be brought about by these assays in conjunction with the findings of ongoing studies.

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