Editorial Commentary

Advances of HER2 testing for women with breast cancer

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Human epidermal growth factor receptor 2 (HER2) over-expression/amplification is seen in 15–20% of newly detected breast cancers (1). HER2 has been a major biomarker of focus for targeted therapy as these types of tumors tend to be aggressive and carry poor prognosis. HER2 targeted therapies have remarkably improved survival outcomes in these patients (1). Understanding the molecular pathways associated with HER2 gene and the human epidermal growth factor (Erb) family-EGFR (ErbB1/HER1), ErbB2 (HER2/Neu), ErbB3 (HER3), ErbB4 (HER4) has been of great interest for researchers for many years. Sequencing studies have identified signal transduction mediated by activation of PI3K/AKT and Ras/Raf/MEK/MAPK pathways, attribute to adverse biological characteristics and clinical outcomes (2). HER2 status in women with breast cancers, is extremely important and false positive or negative testing can alter the treatment and prognosis (3). Both immunohistochemistry (IHC) and fluorescent in-situ hybridization (FISH) assay currently test for HER2 status across laboratories. College of American Pathologists (CAP)/American society of Clinical Oncology (ASCO) approved testing methodologies and scoring system have been established as standard and their periodic updates were an essential step in standardizing practices (4-6). However, we have observed in our study that several adjustments in scoring criteria of IHC and in-situ hybridization (ISH) as they were updated, created challenges in interpretation among the pathologists (3). In the same study, we observed the studies that reported the impact of guidelines applied the modified ASCO/CAP guidelines from 2013 which resulted in an increase (2%) in the overall HER2 positive rate compared to applying 2007 ASCO/CAP guidelines. The increased positivity rate was mostly due to more FISH-positive cases (3.5%). The high rate of equivocal cases (4.1%) did not contribute to an increase in overall HER2 positivity but resulted in delay in definitive HER2 status. The recently updated guidelines have made significant changes in eliminating the "equivocal category", and uncommon ISH patterns are subjected to a more rigorous evaluation along with HER2 IHC and categorized them into special clinically significant groups. As the impact of 2018 guidelines data is emerging, few studies have reported a high percentage of HER2 negative cases. The reclassification of the equivocal results most probably contributed up to 6% for the significantly increased rate of negative results. It also was reported by Gordian-Arroyo *et al.* that HER2-positive rate decreases by 0.4% (3,6,7).

HER2 testing in pathology practices in community and academic hospitals is widely diverse.

The concordance between local and central laboratory HER2 IHC testing was observed to be highest for local IHC 3+ and lowest for IHC 2+ samples (77% *vs.* 26%). Thirty-three percent (33%) of samples interpreted as IHC 2+ at local laboratories tested FISH-positive at the central laboratory. Concordance between HER2 IHC and FISH results was observed to be higher when both tests were performed at the central laboratory (8,9).

Chinese Society of Clinical Oncology (CSCO) recently published their consensus based on recent evidence, led by group of expert oncologists and surgeons (10). The efficacy of newer HER2 drugs like pertuzumab in addition

to trastuzumab and chemotherapy were addressed based on a variety of clinical trial data. A comprehensive review of various trials on anti-HER2 treatments in neoadjuvant and metastatic setting were discussed. Recently emerging HER2-low treatments were discussed. The study emphasized the importance of testing and re-testing HER2 in laboratories that has diagnostic as well as prognostic implications (10). One of the highlights of the article was addressing the successful management of breast cancer patients during public health emergencies like coronavirus disease 2019 (COVID-19) pandemic. Recommendations for the triage and treatment of women with breast cancer amidst the COVID-19 pandemic were published by American Society of Breast Surgeons (ASBS) to provide highest quality of care (11,12).

Recently, the DESTINY-Breast04 clinical trial demonstrated that targeting HER2 provides significant benefits for patients with metastatic breast cancer (MBC) with low levels of HER2 expression, i.e., IHC score 1+ or ISH-negative IHC score 2+. In this randomized clinical study, the antibody-drug conjugate (ADC) trastuzumab deruxtecan (T-DXd) improved median progression-free survival by 4.8 months and median overall survival by 6.6 months, compared with standard single-agent chemotherapy. Based on the trial results, FDA recently approved Enhertu (trastuzumab-deruxtecan) as an IV infusion for unresectable or metastatic HER2-low breast cancers. The proposed definition of the HER2-low breast cancers appears to be breast cancers with the HER2 immunohistochemistry score of 1+/2+ with the concurrent negative ISH result (13,14). A near future the concept and definition of HER2-low based on the ongoing clinical trials and studies to be defined daily for the pathologists by CAP/ASCO.

In conclusion, in the era of therapeutic armamentarium, the spectrum of HER2 testing is becoming challenging due to emerging new sub-set categories. The accuracy of HER2 testing in laboratories by immunohistochemistry need strong standardized protocols such as using appropriate tissue controls, newer proficiently testing. Education for the pathologists as well as oncologists and reporting of newly evolving entity of HER2-low biopsies or resection specimens is mandated.

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