Perspective

To treat or not to treat: HER2 equivocal is the matter!

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Abstract: With the introduction of the 2013 American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for human epidermal growth factor receptor type 2 (HER2) testing, some authors noticed an increase in equivocal HER2 determinations. Indeed, many retrospective assessments showed an increase of up to 14% in the number of equivocal cases by immunohistochemistry and fluorescence in situ hybridization. In these cases, if after reflex testing with the same and/or an alternative specimen the HER2 test result is deemed to be equivocal, the ASCO/CAP guidelines recommend to consider HER2-targeted therapy. However, due to the absence of prospective data on the efficacy of anti-HER2 therapy in equivocal HER2 breast cancer (BC), the therapeutic decision is extremely complex, especially in the adjuvant and neoadjuvant settings. In this perspective paper, we analyse the available retrospective data aiming to answer to the dilemma whether to treat or not to treat HER2 equivocal cases with a HER2-targeted therapy.

Keywords: Human epidermal growth factor receptor type 2 (HER2); equivocal; American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP); target therapy

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Human epidermal growth factor receptor type 2 (HER2) is overexpressed in about 15% to 20% of invasive breast cancers (BCs) and is related with modest clinical outcome (1,2). In the adjuvant setting prospective and randomized clinical trials involving trastuzumab (the first humanized monoclonal antibody that binds HER2) plus chemotherapy showed approximately a 50% reduction in risk of recurrence and an improvement of overall survival in HER2-positive BC patients (3-6). Even in the metastatic setting, the introduction of several anti-HER2 treatments significantly improved the prognosis of HER2-positive BC patients (7-9). Given these evidences, HER2 status determination for newly diagnosed invasive BCs is now mandatory in order to select the best treatment (10). After the introduction into clinical practice of trastuzumab, it quickly became evident that HER2 test was subject to important discrepancy between laboratories, leading to divergent results in up to 20% of cases (11). Therefore, in 2007, the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) panel developed guidelines to enhance the precision of HER2 testing in BC (12). Regardless of significant accent on advance made to standardize HER2 test after promulgation of the ASCO/CAP guidelines in 2007, many reports persist to demonstrate absence of concordance for interlaboratory HER2 results (13). Since then, clarifications and updates to these guidelines have been released and in 2013 the ASCO/CAP conducted a formal and comprehensive review (14). In this version, the authors change the immunohistochemical features to assess HER2 protein overexpression, keeping the classification into two major groups: HER2-positive (score 3+) and HER2-negative (score 0 and 1+). In case of equivocal HER2 expression (score 2+), HER2 positivity must be validated by fluorescence *in situ* hybridization (FISH). Using FISH, HER2 positivity is defined by a *HER2* gene copy number ≥6 or a *HER2* gene to chromosome 17 (HER2/CEP17)

ratio≥2.0, while HER2 negativity is considered in case of a *HER2* copy number <4 and a HER2/CEP17 ratio <2. BCs with a *HER2* copy number of 4–6 and a HER2/CEP17 ratio <2 are defined as HER2 equivocal. Moreover, the authors state that "if the HER2 test result is ultimately deemed to be equivocal, even after reflex testing with an alternative assay, the oncologist may consider HER2-targeted therapy".

With the introduction of the 2013 ASCO/CAP guidelines, some authors noticed an increase in equivocal HER2 determinations (15-18). Indeed, many retrospective assessments published in the last years showed an increase of up to 14% in the number of equivocal cases (15). Moreover, our institutional experience matches with these observations. The absence of prospective data on the efficacy of anti-HER2 therapy in equivocal HER2 BCs and the consequent omission of clear recommendations by the ASCO/CAP, make the therapeutic decision extremely complex, especially in the adjuvant and neoadjuvant settings. Waiting for the results of the NSABP-B47 trial, that will assess the impact in terms of invasive disease-free survival (IDFS) of the addition of trastuzumab to chemotherapy in patients with low expression of HER2, we should base our therapeutical choice on retrospective evidences.

Recently, Criscitiello *et al.* retrospectively analyzed 455 consecutive early BC patients with a HER2 score 2+ and a HER2/CEP17 ratio <2.0 and reported no significant link between recurrence risk and HER2 equivocal result (19). Furthermore, in a retrospective analysis presented at the 2016 ASCO meeting, Landmann *et al.* analyzed 595 patients who underwent to neoadjuvant treatment from 2010 to 2014. By histological re-evaluation according to the 2013 ASCO/CAP criteria, 46 patients with HER2 equivocal were identified, 31 of them were considered HER2-positive with the previous 2007 ASCO/CAP evaluation and had received trastuzumab therapy. Interestingly, the rate of complete pathological response (pCR) in HER2 equivocal BCs was equivalent to that of HER2-negative BCs (pCR 16% versus 18%), being much lower than that achieved in confirmed HER2-positive BCs (pCR 41%) (20).

Given these considerations and lacking a clear indication by guidelines, we believe that the Hamletic doubt "to treat or not to treat" HER2 equivocal BCs with anti-HER2 therapy should be addressed for now with no indication for HER2-targeted therapy.

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Footnote

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