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HER2-Low Breast Cancer: Prognosis and Future Treatment Prospective

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The human epidermal growth factor 2 (HER2) is a tyrosine kinase belonging to the Human Epidermal Receptor family [1]. HER2 is amplified leading to HER2 overexpression in 15% of breast cancers (BC) [2]. HER2 overexpression leads to poor prognosis but offers the unique possibility to use a targeted therapy with monoclonal antibodies. This therapeutic option has radically changed the history of HER2 BC [3]. HER2 overexpression represents at present the most powerful predictive factor for likeliness of response to anti-HER2 agents [5].

The HER2 status is routinely assessed either using immunohistochemistry (HER2 protein expression level) or in situ hybridization (HER2 gene status) [2,5,6]. For the purpose of HER2 assessment, international guidelines have been developed by experts in the field and have changed over the years according to new data. HER2 heterogeneity is linked to the complexity of equivocal results, HER2 mutations and the upcoming category of HER2-low BC [7].

Intratumor genetic heterogeneity interests various types of human cancers, including BC andHER2 overexpression and amplification, and it is demonstrated to be significantly more common in cases with HER2 equivocal status [8]. Equivocal cases frequently feature low levels of HER2 amplification. Several studies showed that HER2 heterogeneity is related to poor outcome, shorter disease-free survival and overall survival.Patients with HER2 heterogeneity are less responsive to target therapies as confirmed by a lower achievement of pathologic complete response following neoadjuvant treatment [9].

In spite of the scarcity of data still available on HER2-low BC, different intrinsic subtypes seem to influence different clinical behavior and response to treatment, as this has already been proved for other BC subtypes. HER2-low/HR- BC showed a higher frequency of HER2-enriched instrinsic subtype than HER2-/HR- BC. This might mean that, despite in clinical practice HER2-low/HR- BC is considered as HER2-/HR, these subtypes of BCs might reflect a different clinical behavior and a different response to targeted therapy [10]. Recent studies underlined that HER2-enriched instrinsic subtype are the most beneficial in reduction of risk of progression and death after CDK6/6-inhibitors treatment, compared to the other subtypes [11].

Traditionally HER2-positive BCs were separated from HER2-negative BCs, based on solid clinical data stating that only tumors driven by HER2 oncogene addition benefit from targeted therapies [12]. However in recent years new therapies have

been developed, in particular the antibody drug conjugates which deliver chemotherapy inside the BC. Some of these agents - such as trastuzumab duocarmazine and trastuzumab deruxtecan showed encouraging response rates also in the so called HER2-low BC. For example, the phase 1 study of DS-8201 showed an overall response rate of 37% in pretreated HER2-low metastatic cancer patients, with a median duration of response of 10.4 months [13].

These data suggests a paradigm shift in the definition of HER2 status, which may be based on 3 groups:

i) HER2-positive,
ii) HER2- negative,
iii) HER2-low BCs,

that may potentially benefit from a targeted therapy, even in absence of the addition of the tumor cells to the HER2 oncogene [7].

At present there are no formal definitions of HER2-low BC, but it seems reasonable to define as HER2-low all BCs displaying a score of 1+ or 2+ HER2 expression and no HER2 amplification. This assumption would categorize up to 55% of BCs as HER2-low. For this subtype there are no targeted therapies approved [7].

The majority of HER2 somatic mutations found in BCs have not been associated with HER2 gene amplification. However preclinical data suggest that functionally active HER2 mutations may lead to HER2 targeted therapies sensitivity [14]. Other preclinical models suggest that pertuzumab inhibits tumor proliferation even in absence of HER2 overexpression [15].So, HER2 mutation-positive but HER2-negative BC may benefit from targeted drugs, but further studies are needed. For example, trastuzumab, deruxtecan, a novel enzyme-cleavable linker, showed significant objective response and disease control in a group of patients including 25% HER2-low BCs, and therefore is worthy of further studies in this subgroup of patients [16].

The new agents being tested for HER2-low BC patients are antibody drug conjugates deploying anti-HER2 epitopes in their antibody component, but with different cytotoxic warheads and a bi-specific antibody targeting both HER2 and HER3 [17].

In conclusion, the concept of HER2-positive versus HER2-negative disease is changing, including the definition of “HER2-low” BC, against which new therapies such as antibodydrug conjugates may be extremely effective.

References

1. Hayes DF (2019) HER2 and breast cancer - a phenomenal success story. N Engl J Med. 381(13): 1284-1286.

2. Sapino A, Goia M, Recupero D, et al. (2013) Current challenges for HER2 testing in diagnostic pathology: state of the art and controversial issues. Front Oncol. 21(3): 129.

3. Swain SM, Baselga J, Kim SB, et al. (2015) Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 372(8): 724-734.

4. Cardoso F, Kyriakides S, Ohno S, et al. (2019) Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 30 (8):1194-1220.

5. Annaratone L, Sarotto I, Marchio C (2019) HER2 in breast cancer. Springer.

6. Wolff AC, Hammond MEH, Allison KH, et al. (2018) Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/ College of American Pathologists clinical practice guideline focused update. J Clin Oncol. 36 (20): 2105-2122.

7. Marchiò C, Annaratone L, Marques A, et al. (2021) Evolving concepts in HER2 evaluation in breast cancer: Heterogeneity, HER2-low carcinomas and beyond. Semin Cancer Biol. 72 (1): 123-135.

8. Navin N, Krasnitz A, Rodgers L, et al. (2010) Inferring tumor progression from genomic heterogeneity. Genome Res. 20 (1): 68-80.

9. Kurozumi S, Padilla M, Kurosumi M, et al. (2016) HER2 intratumoral heterogeneity analyses by concurrent HER2 gene and protein assessment for the prognosis of HER2 negative invasive breast cancer patients. Breast Cancer Res Treat. 158 (1): 99-111.

10. Modi S, Park H, Murthy RK, et al. (2020) Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients with HER2-Low–Expressing Advanced Breast Cancer: Results From a Phase Ib Study. J Clin Oncol. 38 (17): 1887-1896.

11. Prat A, Chaudhury A, Solovieff N, et al. (2021) Correlative biomarker analysis of intrinsic subtypes and efficacy across the MONALEESA Phase III studies. J Clin Oncol. 39 (13): 1458-1467.

12. ehrenbacher L, Cecchini R, Geyer C, et al. (2018) NSABPB-47(NRGoncology): phase III randomized trial comparing adjuvant chemotherapy with adriamycin (A) and cyclophosphamide (C) → weekly paclitaxel (WP), or docetaxel (T) and C with or without a year of trastuzumab (H) in women with node-positive or high-risk node-negative invasive breast cancer (IBC) expressing HER2 staining intensityof IHC 1+ or 2+ with negative FISH (HER2-Low IBC). J Clin Oncol. 38 (5): 444-453.

13. Modi S, Park H, Murthy RK, et al. (2020) Antitumor activity and safety of trastuzumab deruxtecan in patients with HER2-Low-Expressing advanced breast cancer: results from a phase Ib study. J Clin Oncol. 38 (17): 1887-1896.

14. Connell CM, Doherty GJ, (2017) Activating HER2 mutations as emerging targets in multiple solid cancers. ESMO Open. 2 (5): e000279.

15. Gianni L, Llado A, Bianchi G, et al. (2010) Open-label, phase II, multicenter, randomized study of the efficacy and safety of two dose levels of Pertuzumab,a human epidermal growth factor receptor 2 dimerization inhibitor, in patients with human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol. 28 (7): 1131-1137.

16. Doi T, Shitara K, Naito Y, et al. (2017) Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS- 8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophagealtumours: a phase 1 dose-escalation study. Lancet Oncol. 18 (11): 1512-1522.

17. Ogitani Y, Aida T, Hagihara K, et al. (2016) DS-8201a, A Novel HER2-Targeting ADC with a Novel DNA Topoisomerase I Inhibitor, Demonstrates a Promising Antitumor Efficacy with Differentiation from T-DM1. Clin Cancer Res. 22 (20): 5097-5108.