De-escalation of treatment in HER2-positive breast cancer: Determinants of response and mechanisms of resistance

Jamunarani Veeraraghavan, Carmine De Angelis, Jorge S. Reis-Filho, Tomás Pascual, Aleix Prat, Mothaffar F. Rimawi, C. Kent Osborne, Rachel Schiff

**A R T I C L E   I N   P R E S S**

The human epidermal growth factor receptor 2 (HER2/ERBB2) is a key member of the HER family consisting of four receptor tyrosine kinases (HER1-4). This family together governs a complex and redundant downstream signaling network that regulates cell survival and metastasis. Despite treatment with effective HER2-targeted therapies, many HER2-positive tumors fail to respond, or initially respond but eventually develop resistance. One of the upfront reasons for this treatment failure is failure to accurately select the tumors that are truly HER2-addicted (i.e., physiologically dependent), as resistance could be the result of an incomplete inhibition of signaling at the HER receptor layer. In this regard, preclinical and clinical studies have documented the superiority of combination anti-HER2 therapy over single agent therapy to achieve a more comprehensive inhibition of the various HER receptor dimers. HER2 can be further activated or reactivated by mutations or other alterations in HER2 itself, or in other HER family members. Even when a complete and sustained HER inhibition is achieved, resistance to anti-HER therapy can arise by other mechanisms, including preexisting or emerging alternative signaling pathways such as the estrogen receptor, deregulated downstream signaling components, especially of the PI3K pathway, and the tumor immune microenvironment. Most of the clinical trials that have investigated the efficacy of anti-HER2 therapies took place in the background of aggressive chemotherapy regimens, thus confounding the identification of key factors of resistance to the anti-HER2 treatments. Recent studies, however, have suggested that some HER2-amplified tumors may benefit from anti-HER2 therapy combined with only a single chemotherapy agent or in the absence of any chemotherapy. This de-escalation approach, a promising therapeutic strategy, is currently being explored in the clinic. In this review, we summarize the major molecular determinants that play a crucial role in influencing tumor response and resistance to HER2-targeted therapy, and discuss the growing need for patient stratification in order to facilitate the development of de-escalation strategies using HER2-targeted therapy alone with no chemotherapy.

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redundant signaling process to regulate cell proliferation, survival, and metastasis [1,2]. The HER family receptors are activated by multiple ligands with the exception of HER2, which has no known ligand but can be activated by heterodimerization with other ligand-bound HER receptors or by homodimerization in tumors expressing high levels of HER2. HER2 overexpression, largely due to gene amplification, is observed in about 15–20% of breast cancers, known as HER2-positive, and accounts for their aggressive and metastatic behavior. Multiple HER2-targeted therapies, including humanized monoclonal antibodies such as trastuzumab and pertuzumab, and tyrosine kinase inhibitors such as lapatinib, have been developed, with trastuzumab being the first to be FDA-approved [1,2]. Though highly effective in patients, especially in combination with aggressive chemotherapy, intrinsic and acquired resistance to trastuzumab and other HER2-targeted drugs still occurs and remains clinically challenging. Trastuzumab by itself, with no chemotherapy, is much less effective [1] as it only partially inhibits HER2 signaling, although it also activates antibody-dependent cell-mediated cytotoxicity (ADCC) [1]. One major plausible mechanism responsible for resistance is incomplete inhibition of the HER receptor layer, particularly considering the functional redundancy of signaling from multiple HER receptor dimers and compensatory signaling within the pathway [3]. This suggests that dual inhibition of the combination of trastuzumab or lapatinib with trastuzumab might achieve a more complete blockade of HER2 signaling. To that end, the superiority of dual anti-HER2 therapy over single-agent treatment has been established in the clinic in both the neoadjuvant and metastatic settings, although most of the clinical trials were done in the presence of chemotherapy [4,5]. We and others have proved the concept that combining HER2-targeted agents without concomitant chemotherapy can produce complete tumor eradication in preclinical HER2-positive breast cancer mouse models [6–8]. These findings led to several neoadjuvant clinical trials with similar treatments of dual HER2 inhibition with no chemotherapy, which have yielded substantial pathologic complete response (pCR) [9–11]. These results suggest that a subset of patients with HER2-amplified tumors may not need chemotherapy at all. It is therefore essential to identify upfront those patients who can be spared chemotherapy, as well as to understand the mechanisms of resistance in order to devise more effective tailored treatments. The various mechanisms of resistance to anti-HER2 therapy have been comprehensively reviewed in the last few years [12–15]. In this review, our focus is to summarize the major molecular determinants that play a crucial role in influencing tumor response and resistance to HER2-targeted therapy, and to discuss the rationale and clinical significance of patient stratification for successful HER2-targeted therapy without chemotherapy.

2. Major contributing factors of response and resistance to HER2-targeted therapy

The response of a tumor to HER2-targeted therapy primarily depends on HER2 expression level and how much the tumor is dependent on HER2 for its existence. Emerging evidence further suggests that the HER2 therapy response is also governed by a multitude of other factors. The principal determinants of HER2 therapy response and resistance can be largely grouped into four major categories (Fig. 1). The first category is HER2 itself, since a tumor will best respond to anti-HER2 therapy, especially without chemotherapy, only when it exhibits absolute dependence (oncogene addiction) on HER2 for sustained proliferation and survival, which is associated with high levels of HER2 gene amplification, RNA expression, and downstream signaling (Fig. 1A). Despite successful HER2-targeted therapy, HER2-addicted tumors can develop resistance due to reactivation of the signaling pathway via HER2 itself or other compensatory mechanisms within the HER receptor layer, which may be pre-existing at the time of treatment or acquired in due course. The second category includes additional alternative signaling pathways, pre-existing or acquired, that provide compensatory signaling to offset and overcome the inhibitory effects of HER2-targeted therapy. One leading member of this category is estrogen receptor (ER) signaling (Fig. 1B). This is particularly crucial in HER2-positive tumors that are also hormone receptor (HR)-positive. The third category is deregulation of downstream signaling components in the HER signaling pathway, especially the PI3K/PTEN pathway, one of the major downstream components of HER signaling (Fig. 1C). The fourth and most recently revisited category is the tumor immune microenvironment (Fig. 1D). Each of the categories mentioned above is comprised of multiple eminent players. However, in this review, we will focus on discussing the significance of a key and more prevalent component in each category that has been characterized preclinically and suggested to play a role in the clinical setting.

3. Oncogenic HER2 addiction

One of the principal determining factors of response to anti-HER2 therapies is the extent to which the cancer cells within a HER2-positive breast cancer are dependent on HER2 itself for the maintenance of their malignant phenotype. This dependency is termed oncogene addiction, and such tumors respond best to drugs targeting the oncogene they are addicted to [16]. High and homogeneous levels of HER2 gene amplification, expression of HER2 mRNA and protein, and HER2 downstream signaling are necessary for true HER2 addiction, and identification of HER2-addicted tumors is essential to reap the complete therapeutic benefit of HER2-targeted drugs. In this regard, methods and defined cutoffs to accurately identify the true HER2-addicted tumors with high HER2 expression and signaling activity are critical. Indeed, recent studies suggest that high HER2 mRNA levels and the PAM50-classified HER2-enriched subtype are associated with a better response to HER2 therapy both with [17] and without chemotherapy [10]. Additionally, the key role of intra-tumor HER2 amplification heterogeneity in HER2-targeted therapy resistance has been recently shown [18], which further emphasizes the need for homogeneous HER2 amplification to achieve an effective response to HER2-targeted therapy. It is expected that the cutoff needed to identify truly HER2-addicted tumors that will benefit from HER2-targeted therapy without chemotherapy may be higher than the current guidelines in place, which aim to identify those patients who may benefit from adding HER2-targeted treatment to chemotherapy [19]. In this regard, we need to investigate and compare several leading methods and cutoffs to redefine HER2 status at various levels including HER2 copy number, mRNA, and protein, as well as by intrinsic HER2-enriched subtype by the PAM50 molecular subtyping classification. It is important to understand that the tumors that do not meet this higher cutoff may still benefit from and need HER2-targeted therapy but these will not be considered as the true HER2-addicted tumors.

Even in these HER2-addicted tumors, intrinsic and acquired resistance to HER2-targeted therapy is still common. This can occur at various molecular levels including HER2 itself or other HER family members. HER2 mutations, mostly activating, have been reported in both HER2-positive and negative tumors in~3% of breast cancer [The Cancer Genome Atlas Study (TCGA) by cbioPortal] [20,21]. These activating mutations play a key role in activating HER2 signaling, including in HER2-negative tumors, but also influence response and resistance to HER2-targeted therapy, and therefore may nullify the therapeutic effect of various HER2-targeted agents [22]. Two recent studies by Boulbes et al. and Zuo...
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