The Breast 39 (2018) 80–88

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

HER2-positive breast cancer: Current and new therapeutic strategies

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ARTICLE INFO

Article history:
Received 22 December 2017
Received in revised form
11 March 2018
Accepted 19 March 2018

Keywords:
HER2 positive
Targeted therapies
Drugs in development
Advanced breast cancer

ABSTRACT

Since the identification of the HER2 receptor amplification as an adverse prognostic factor that defined a special subtype of metastatic breast cancer, there has been a substantial improvement in survival of patients affected with this disease due to the development of anti-HER2 targeted therapies. The approval of trastuzumab and pertuzumab associated to a taxane in first line and subsequent treatment with the antibody-drug conjugate T-DM1 has certainly contributed to achieve these outcomes. The Tyrosine Kinase Inhibitor lapatinib was also approved in the basis of an improvement in progression free survival, becoming another commonly used treatment in combination with capecitabine. Inevitably, despite these therapeutic advances most patients progress on therapy due to primary or acquired resistance or because of an incorrect HER2 positivity assessment. Hence, it is crucial to correctly categorize HER2 amplified tumors and define mechanisms of resistance to design effective new treatment approaches. In addition, identifying biomarkers of response or resistance permits to tailor the therapeutic options for each patient sparing them from unnecessary toxicity as well as improving their outcomes. The aim of this review is to examine new strategies in development to treat HER2-positive metastatic breast cancer referring to the mechanisms of action of new drugs and new combinations including results reported so far.

1. Introduction

Breast cancer is the most common cancer in women and still the second leading cause of death in developed countries despite the advances made in the field over the last years [1]. The prognosis of breast cancer has improved since the developing of targeted therapies especially considering the HER2-positive subtype, but advanced cancer continues to be considered mostly an incurable disease and survival may diverge widely among patients [2]. Defining cure as when the overall survival for a metastatic population approaches that of an age and sex-matched general population, optimizing therapy would permit to have more exceptional responders who achieve this goal [3]. About 15–20% of all breast cancers are considered HER2-positive because of the overexpression of this receptor and about 50% of these will also have expression of estrogen and/or progesterone receptors (ER/PR) [4].

Accurate assessment of HER2 status is essential in treatment decision-making for patients with breast cancer. False-negative HER2 status may lead to omission of anti-HER2 directed therapy, and conversely, false-positive HER2 results may lead to needless administration of costly and prolonged treatment with no benefit. There are different methods for assessing HER2 amplification but the most validated ones that are used both in clinical practice and in clinical trials are still immunohistochemistry (IHC) and in situ hybridization. The American Society of Clinical Oncology (ASCO) published guidelines on HER2 testing for breast cancer in 2013 that recommend performing HER2 testing on every new diagnosed invasive breast cancer and also in recurrent disease if there is specimen available. According to the guidelines, HER2 testing should be done by IHC or single- or dual-probe in situ hybridization (ISH) test with specific criteria for interpreting results. Therefore, a tumor is determined as HER2-positive if the number of tumor cells displaying strong overexpression (3 + cells) exceeds 10% of the total tumor population; equivocal if the number of tumor cells displaying moderate HER2 overexpression (2 + cells) exceeds 10% of the total tumor population and negative otherwise. If initial HER2 result is equivocal by IHC, then an ISH assay should be performed to confirm HER2 status [5]. Despite having well defined cut-off points and threshold for considering HER2 amplification there is still a need to better define which tumors are really dependent on this pathway since there might be discordance among different techniques and observers. Compelling studies have indicated that discordance in HER2 testing between local and central laboratories

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https://doi.org/10.1016/j.breast.2018.03.006
0960-9776/

in clinical trials has been reported to be as high as 20% for IHC and 12% for FISH [6]. HER2-addicted tumors exhibit absolute dependence on the HER2 pathway for sustained proliferation and survival, associating high levels of HER2 gene amplification, RNA expression and downstream signaling. Other methods for determining HER2 positivity are PAM50, mRNA expression, mass spectrometry and also determination of levels of circulating HER2 [7]. These methods, not yet validated for clinical practice, are important as potential techniques for identifying tumors as HER2-dependent. Such tumors respond best to drugs targeting the oncogene they are addicted to. In this setting, the PAMELA trial revealed that the HER2-enriched molecular subtype (determined by PAM50) within HER2-positive breast cancer was associated with 41% pathological complete response rate (pCR) in the absence of chemotherapy, following neoadjuvant double HER2 blockade with lapatinib and trastuzumab, adding also endocrine therapy if hormone receptor-positive (HR-positive); whereas pCR was 10% in patients non-HER2-enriched subtype at baseline [8].

Research into HER2-targeting agents has been one of the most productive areas of oncologic drug development. In general, HER2-targeting can be classified under two potentially overlapping mechanistic categories: the first includes drugs that use HER2 overexpression as a tumor cell identifier to deliver tumoricidal effectors to cancer cells. These include HER2 antibodies and their derivatives. The second category includes drugs that treat the disease by inhibiting the oncogenic signaling function of HER2. Drugs in this class predominantly include the tyrosine kinase inhibitors (TKIs) [9].

In the first category, the overexpression of HER2 on the cell surface of HER2-positive cancers provides an ideal target that enables the delivery of cancer-killing agents to cancer cells with great selectivity, by specific anti-HER2 antibodies. Trastuzumab and pertuzumab belong to this class of antibodies that among their mechanisms of action include antibody-dependent cellular cytotoxicity (ADCC), enhancing the recruitment of immune innate effector cells to mediate tumor lysis dependent on expression of Fc receptors (FcRs). Another approach is the delivery of potent toxins in the form of antibody-drug conjugates (ADCs) such as trastuzumab-emtansine (T-DM1) [10].

In the second category, HER2 signaling can be inhibited using oral TKIs, such as lapatinib, neratinib, afatinib, and others currently in development. These small molecules compete for the adenosine triphosphate binding domain within the cytoplasmic portion of the HER2 receptor preventing phosphorylation and subsequent activation of the signaling transduction pathways, decreasing cell proliferation and promoting apoptosis [11].

Trastuzumab was the first anti-HER2 agent approved by the FDA for clinical use after a landmark randomized trial in 1998 demonstrated that the addition of the antibody to chemotherapy led to improved progression-free survival (PFS) and overall survival (OS) in patients with HER2-positive metastatic breast cancer (MBC) [12]. Interestingly, while trastuzumab has modest activity as monotherapy (objective response rate 23%–35% in patients with confirmed HER2-positive MBC), its ability to synergistically improve the efficacy of chemotherapy has led to the combination of trastuzumab and chemotherapy being the preferred approach in most settings [13,14]. Several phase III studies demonstrated considerable improvements not only in the metastatic setting but also in disease-free survival (DFS) and OS in patients with curable disease [15–17].

The results with trastuzumab provided clinical proof of concept that targeting HER2 could substantially improve outcomes in patients with HER2-positive cancers and provided the motivation for the development of other anti-HER2 agents. The first of these was lapatinib, an orally administered TKI, small-molecule, reversible inhibitor of the HER2 and EGFR Kinases. A pivotal phase III study compared lapatinib and capecitabine combination therapy with capecitabine alone in patients with HER2-positive MBC who previously had received trastuzumab and chemotherapy. The addition of lapatinib was associated with improved PFS, although with no significant effect on OS, compared with capecitabine alone, leading to FDA approval of lapatinib in this setting [18].

More recently, two antibody-based therapies were approved by the FDA: pertuzumab and T-DM1. Pertuzumab was selected for development because its epitope lies on the dimerization interface of HER2, mostly preventing the pairing of the most potent heterodimer HER2/HER3. Thus, this drug enhanced the clinical activity of trastuzumab. This effect was confirmed in the randomized phase III CLEOPATRA study, in which 808 patients with HER-2 positive MBC were randomized 1:1 to either docetaxel, trastuzumab, and placebo (DT) or to docetaxel, trastuzumab, and pertuzumab (DTP) in the first-line setting. With a median follow-up of 50 months, patients who received DTP demonstrated a superior median progression-free survival (HR 0.68) and a substantial difference of 15.7 months in overall survival (HR, 0.68) [19]. Of note, mainly due to the historical context, most patients included in the trial were trastuzumab naïve. Among the 47 patients in the pertuzumab group and 41 patients in the placebo group who had previously been treated with trastuzumab, the HR: 0.80 for death from any cause was not significant. Notwithstanding, the trial was underpowered for this exploratory analysis. This pivotal study altered the paradigm in the first-line treatment of patients with HER2-positive MBC, for which trastuzumab with a taxane plus pertuzumab is the preferred approach [20,21].

TDM- 1 consists of a potent cytotoxic agent linked to trastuzumab, exploiting HER2 overexpression on the surface of HER2-positive cancers to selectively deliver high levels of the toxin to these cells. T-DM1 was approved by the FDA in 2013 for use in patients with HER2-positive MBC that had progressed under treatment with trastuzumab and a taxane. This approval was based on the results of the randomized phase III EMILIA study that demonstrated TDM-1 superiority over capecitabine plus lapatinib in PFS (HR, 0.65) and OS (HR, 0.68) [22]. Of note, upon progression beyond second-line therapies, if the patient has not received T-DM1, this therapy is recommended based in the significant PFS (HR 0.528) and OS (HR 0.68) benefits shown in the TH3RESA trial that randomized patients to T-DM1 or physician's treatment choice [23].

First line T-DM1 was explored in the MARIANNE trial that randomly assigned patients with progressed or recurrent locally advanced or previously untreated metastatic HER2-positive breast cancer to trastuzumab plus taxane: docetaxel or paclitaxel, T-DM1 plus pertuzumab or T-DM1 plus placebo. T-DM1 and T-DM1 plus pertuzumab showed neither superior PFS nor OS compared with trastuzumab plus taxane that represented the standard of care for this population at the time the study was initiated [24]. Thus, T-DM1 is not a preferred first-line treatment except for patients that relapse during trastuzumab adjuvant therapy or early after its completion based in the EMILIA trial inclusion criteria [20,21].

Multiple treatment options are available when disease progresses after second-line therapies or T-DM1. Feasible options include lapatinib plus capecitabine, as well as other combinations of chemotherapy and trastuzumab such as vinorelbine, gemcitabine and capecitabine; double blockage with lapatinib and trastuzumab, or even endocrine therapy (in patients with HR-positive disease) [25–27]. There is insufficient evidence to recommend one regimen over another. Any of these alternatives seems acceptable whenever any anti-HER2 agent is part of the combination [20,21].