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Review

Evolving landscape of human epidermal growth factor receptor 2-positive breast cancer treatment and the future of biosimilars

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ABSTRACT

Human epidermal growth factor receptor 2-positive (HER2+) breast cancer comprises approximately 15%–20% of all breast cancers and is associated with a poor prognosis. The introduction of anti-HER2 therapy has significantly improved clinical outcomes for patients with HER2+ breast cancer, and multiple HER2-directed agents (ie, trastuzumab, pertuzumab, lapatinib, and ado-trastuzumab emtansine [T-DM1]) are approved for clinical use in various settings. The treatment landscape for patients with HER2+ breast cancer is continuing to evolve. While novel agents and therapeutic strategies are emerging, biologic therapies, particularly trastuzumab, are likely to remain a mainstay of treatment. However, access issues create barriers to the use of biologics, and there is evidence for underuse of trastuzumab worldwide. A biosimilar is a biologic product that is highly similar to a licensed biologic in terms of product safety and effectiveness. Biosimilars of trastuzumab are in development and may soon become available. The introduction of biosimilars may improve access to anti-HER2 therapies by providing additional treatment options and lower-cost alternatives. Because HER2-targeted drugs may be administered for extended periods of time and in combination with other systemic therapies, biosimilars have the potential to result in significant savings for healthcare systems. Herein we review current and emerging treatment options for, and discuss the possible role of biosimilars in, treating patients with HER2+ breast cancer.

Contents

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1. Introduction

Breast cancer is the most common cancer among women worldwide, with an estimated 231,840 new cases diagnosed in the United States and 471,724 in Europe in 2015 [1,2]. Approximately 1.7 million new cases of breast cancer were diagnosed in 2012 worldwide [3] and the global incidence is projected to be over 1.9 million in 2020 [2]. Breast cancer comprises many distinct histological subtypes and is further classified based on the expression of biological markers [4,5].

Approximately 15%–20% of all invasive breast cancers overexpress human epidermal growth factor receptor 2 (HER2) [6–10], a key mediator of cell growth, differentiation, and survival [11]. HER2-positive (HER2+) tumors tend to be of higher histological grade and are more likely to invade axillary lymph nodes (node-positive) than other tumor subtypes [4,5]. These histopathological features give rise to an aggressive tumor subtype that historically was associated with shortened survival and an increased risk of disease recurrence and metastasis [12–14]. However, patients with HER2+ breast cancer are sensitive to and derive significant clinical benefit from HER2-directed agents [15–32]. Therefore, HER2-overexpressing tumors can be targeted directly. Currently, four HER2-directed agents are approved for the treatment of patients with HER2+ breast cancer: trastuzumab, pertuzumab, lapatinib, and ado-trastuzumab emtansine (T-DM1) [33–40]. However, access issues have been reported as a barrier to the use of biologics [41–43], and there is evidence for underuse of trastuzumab worldwide [9,44–53].

The treatment landscape for HER2+ breast cancer is evolving. Novel agents and therapeutic strategies are emerging, but treatment regimens remain focused on targeted therapy with biologics, particularly trastuzumab. Patents for many biologics have expired or will expire within the next few years [54], allowing for the development of biosimilar agents. A biosimilar is highly similar to and has no clinically meaningful differences in safety and effectiveness from a licensed biologic product (ie, reference or originator) [55–57].

The availability of safe and effective biosimilars for HER2-directed biologics may improve access to these critical therapies. For example, trastuzumab biosimilars are in development and may soon become available to patients with HER2+ breast cancer. This review summarizes current standard treatment options and the evolving landscape for patients with HER2+ breast cancer as well as the possible role of biosimilars in treating this disease.

2. HER2+ breast cancer: current treatment options

Current treatments for patients with HER2+ breast cancer include different strategies for inhibiting the HER2 pathway. Trastuzumab and pertuzumab are recombinant humanized monoclonal antibodies that target different epitopes of the HER2 extracellular domain [33–35,39]. Binding of trastuzumab to HER2 inhibits ligand-independent signaling by preventing the formation of HER2 homodimers [33,58]. By contrast, pertuzumab inhibits ligand-dependent signaling by preventing heterodimerization of HER2 with other members of the HER family [35,39,58]. Lapatinib, a small-molecule tyrosine kinase inhibitor (TKI), binds HER1 and HER2 intracellular domains to block activation of their downstream signaling pathways [37,38]. Finally, the antibody-drug conjugate T-DM1 links trastuzumab to the cytotoxin emtansine to inhibit HER2 signaling and to optimize the delivery of chemotherapy [36,40].

The American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN) treatment guidelines for breast cancer recommend the addition of HER2-directed agents to systemic chemotherapy or endocrine therapy for the treatment of patients with early, advanced, and metastatic HER2+ breast cancer (Table 1) [59–63].

Table 1
Summary of American Society of Clinical Oncology, European Society for Medical Oncology, and National Comprehensive Cancer Network treatment guidelines for patients with HER2+ breast cancer.

Setting	ASCO [62,63]	ESMO [59,61]	NCCN [60]
Neoadjuvant/adjuvant	Dox + Cy → Pac (or Doc) + Trast Doc + Carb + Trast Fluor + Epi + Cy → Doc + Trast Dose-dense Dox + Cy → Pac + Trast Pac + Trast[c] Doc + Cy + Trast[c]	Dox + Cy → Taxane + Trast ± Pert[a]	Dox + Cy → Pac (or Doc) + Trast ± Pert[a,b] Doc + Carb + Trast ± Pert[a,b] Fluor + Epi + Cy → Pac (or Doc) + Trast + Pert[a,b] Pac (or Doc) + Trast + Pert → Fluor + Epi + Cy[a,b] Pac + Trast[c] Doc + Cy + Trast
Metastatic			
First line	Trast + Pert + Pac (or Doc)	Trast + Pert + Pac (or Doc)	Trast + Pert + Pac (or Doc)
Second or later line	T-DM1 Trast + Pert ± Cht[d] Lap + Cap Lap + Trast	T-DM1 Trast + Pert ± Cht[d]	T-DM1 Trast + Pert ± Cht[d] Trast + Pac ± Carb Trast + Doc Trast + Vin Trast + Cap Lap + Cap Lap + Trast

ASCO, American Society of Clinical Oncology; Cap, capecitabine; Carb, carboplatin; Cht, chemotherapy; Cy, cyclophosphamide; Doc, docetaxel; Dox, doxorubicin; Epi, epirubicin, ESMO, European Society for Medical Oncology; Fluor, fluorouracil; HER2, human epidermal growth factor receptor 2; Lap, lapatinib; NCCN, National Comprehensive Cancer Network; Pac, paclitaxel; Pert, pertuzumab; Trast, trastuzumab; T-DM1, ado-trastuzumab emtansine; Vin, vinorelbine.

[a] The addition of pertuzumab to adjuvant systemic therapy is recommended as a possible treatment for patients who have not received a pertuzumab-containing regimen as neoadjuvant therapy.

[b] A pertuzumab-containing regimen is recommended by NCCN as neoadjuvant treatment for patients with locally advanced HER2+ breast cancer and for some patients (node-positive or tumor ≥2 cm) with early-stage disease.

[c] May be considered for patients with small (≤1 cm), node-negative HER2+ breast cancer.

[d] A line of therapy containing trastuzumab and pertuzumab with or without cytotoxic chemotherapy may be considered for patients whose disease progressed following prior trastuzumab-based therapy that did not include pertuzumab in the metastatic setting.