Published in final edited form as:
Curr Opin Obstet Gynecol. 2011 February ; 23(1): 37–43.

HER2-Positive Breast Cancer: Current Management of Early, Advanced, and Recurrent Disease

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Abstract

Purpose of review—This review describes the current treatment of human epidermal growth factor receptor-2 (HER2) positive breast cancer with a focus on recently reported clinical trials. Treatment of resistant disease and central nervous system metastases will be reviewed as will new agents that are being developed to target HER2 amplified breast cancers.

Recent Findings—Recent studies evaluating trastuzumab-resistant breast cancer have shown a benefit of continuing trastuzumab with chemotherapy or with another HER2-targeted agent. Targeting the vascular endothelial growth factor (VEGF), mammalian target of rapamycin (mTOR), and PI3 kinase pathways in addition to HER2 may enhance efficacy compared with individual agents. Several novel anti-HER2 compounds are being evaluated with promising early data.

Summary—HER2-positive breast cancer has traditionally been associated with poor prognosis. However, treatment with HER2-targeted therapies has changed the natural history of this disease. Greater success depends on elucidating mechanisms of resistance and exploring new methods of blocking signal transduction via HER2 and related pathways.

Keywords

Breast cancer; HER2; trastuzumab; lapatinib; brain metastases

INTRODUCTION

Breast cancer is the most common female malignancy in the USA and the second leading cause of cancer death in women [1]. It has become evident, through gene expression profiling, that breast cancer is a heterogeneous disease, comprised of at least five subtypes [2]. Approximately 25% of breast cancers are classified as HER2-positive, which denotes an aggressive phenotype [3, 4]. However, with the advent of HER2 targeted therapy, most notably, trastuzumab, the natural history of HER2-positive breast cancer has been dramatically improved [5, 6].

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BIOLOGY OF HER2+ BREAST CANCER

The ErbB family of receptor tyrosine kinases is comprised of four cell-surface receptors, HER1 (epidermal growth factor receptor [EGFR]), HER2, HER3, and HER4. Upon receptor dimerization an intracellular signaling cascade is activated, resulting in cell proliferation, survival, invasion, and angiogenesis (Figure 1). In contrast to the other ErbB family members, no ligand has been identified for HER2 [7]. However, HER2 is the preferred dimerization partner within the ErbB family, a feature which contributes to its importance [8].

The diagnosis of HER2-positive breast cancer is made via immunohistochemistry (IHC), which identifies overexpression of the HER2 gene product and fluorescence in situ hybridization (FISH) analysis, which identifies amplification of the HER2 gene. According to the College of American Pathology (CAP) guidelines, tumors that have indeterminate results by IHC (2+) should have reflex testing by FISH [9]. Some institutions use FISH routinely as it is less subjective than IHC interpretation and is associated with a greater predictive value of response to HER2-directed therapy [10].

Trastuzumab is a humanized murine IgG monoclonal antibody that binds to the HER2 extracellular domain. Its mechanism of action has not been fully ascertained, however, it has been shown to reduce signaling through the PI3K/Akt and Ras/Raf/MEK/MAPK pathways, leading to cell cycle arrest, inhibition of DNA repair after chemotherapy [11] and induction of apoptosis [12]. Two small clinical studies have suggested that trastuzumab may promote antibody dependent cellular cytotoxicity (ADCC), in which the antibody Fc portion is bound to Fc receptors expressed by immune effector cells, such as NK cells [13, 14]. However, a recent analysis of genomic DNA samples from trastuzumab treated breast cancer patients found no significant correlation between FcR genotype and disease free survival (DFS) or progression-free survival (PFS), and, therefore, did not support ADCC as a major mechanism of action of trastuzumab [15].

CURRENT TREATMENT OPTIONS

The following section discusses the current treatment options available.

Metastatic Breast Cancer

The use of trastuzumab with or without chemotherapy is the backbone of systemic treatment of HER2-positive breast cancer. The incorporation of trastuzumab into the treatment of HER2-positive breast cancer was based on a groundbreaking Phase III trial in which 469 women with HER2-positive metastatic breast cancer (MBC) were randomized to receive standard chemotherapy with or without trastuzumab. The addition of trastuzumab extended time to progression (TTP) from 4.6 months to 7.4 months ($p<0.001$) and reduced the relative risk of death by 20% (hazard ratio (HR) 0.80, $p<0.046$) [16].

Single agent trastuzumab has also been evaluated, but yields lower overall response rate (ORR; 15% in treatment-refractory MBC [17]; 30% in the first-line setting [18, 19]) than when combined with chemotherapy. In the past decade, numerous studies have

demonstrated safety and efficacy of various chemotherapeutic agents combined with trastuzumab [20–25]. Cardiotoxicity is unacceptably high with the concurrent use of anthracyclines and trastuzumab and is not recommended [26]. About half of HER2-positive tumors are also estrogen receptor (ER) positive. Patients with HER2-positive, ER-positive breast cancer may derive less benefit from endocrine therapy [27], possibly due to HER2 and ER crosstalk [28]. These findings support strategies that combine endocrine therapy with trastuzumab. In a randomized Phase III trial (the TAnDEM study) the combination of anastrozole and trastuzumab was shown to significantly improve progression free survival (PFS; 4.8 vs 2.4 months) and ORR (20.3% vs 6.8%) over anastrozole alone [29].

Progression on trastuzumab

Despite its remarkable impact on HER2-positive breast cancer, resistance to trastuzumab remains a therapeutic challenge. Trastuzumab resistance from the outset of treatment, known as *de novo* resistance is seen in approximately 50% of patients with MBC and acquired resistance after initial response to trastuzumab develops in most patients. Putative mechanisms of trastuzumab resistance include upregulation of alternative cell signaling pathways [30], expression of a truncated HER2 protein which lacks the trastuzumab binding site [31], and autophagy, in which cancer cells recycle and repackage proteins needed for their survival [32]. Expression of membrane-associated glycoprotein mucin-4 (MUC4), may confer resistance to trastuzumab by masking HER2 [33].

Trastuzumab with chemotherapy after progression

Evidence is emerging that supports continued use of trastuzumab with second- and third-line chemotherapeutic agents after disease progression on trastuzumab [34–36]. The German Breast Group 26/Breast International Group 03–05 trial randomly assigned 156 patients who had progressed on trastuzumab to capecitabine alone versus capecitabine with trastuzumab. Median TTP (8.2 mos vs. 5.6 mos, p=0.0338) and ORR (48.1% vs 27.0%, p=0.0115) were significantly better in the combination arm compared to capecitabine alone [35].

Lapatinib

Lapatinib is an oral, small molecule tyrosine kinase inhibitor that targets both HER2 and EGFR. Since the action of lapatinib is intracellular, it may avoid resistance mechanisms involving the HER2 extracellular domain. Lapatinib is primarily used to treat trastuzumab-resistant tumors based on a Phase III study in which patients pretreated with an anthracycline, taxane, and trastuzumab were randomized to receive capecitabine and lapatinib versus capecitabine alone. A significant improvement in ORR and TTP was seen with the combination regimen. However, there was no difference in overall survival (OS) [37]. Lapatinib monotherapy for patients who progress on trastuzumab is well tolerated, but only of modest benefit. In a Phase II study of 78 women with heavily pretreated HER2-positive breast cancer, ORR was 5.1% and clinical benefit rate was 9% for single agent lapatinib [38].

Brain metastases

Brain metastases have become more common as the initial site of recurrence as patients live longer. One study suggests that nearly 50% of patients treated with trastuzumab develop brain metastases [39]. Their development may relate to biologic characteristics specific to HER2-amplified malignancies [40–42]. Local therapies including surgery, whole brain radiation, and stereotactic radiosurgery have been the primary approach to treating central nervous system (CNS) metastases. However, results of systemic treatment of brain metastases in HER2-positive breast cancer have been disappointing, likely due to the inability of systemic therapies, including trastuzumab, to cross the blood brain barrier (BBB) [40]. In spite of this, there is evidence that continuing trastuzumab beyond CNS progression improves outcomes [43] and patients with HER2-positive CNS metastases do appear to live longer than those that are HER2-negative [44].

Lapatinib is a small molecule with the ability to cross the BBB making it an attractive candidate for the treatment of CNS metastases. In the original Phase III study of lapatinib and capecitabine, an exploratory analysis demonstrated a decrease in CNS relapse in lapatinib treated patients [45]. While a Phase II study of lapatinib in 39 HER2-positive patients with brain metastases did not meet its primary endpoint of objective tumor response, volumetric decrease in CNS lesions suggested that lapatinib did have activity [46]. This finding prompted another Phase II study of 242 patients with CNS metastases treated with lapatinib. A modest 6% of patients responded. However, of 50 patients who entered an extension phase of the study in which capecitabine was added to lapatinib, 20% responded [47]. Studies combining lapatinib with cytotoxic chemotherapy and other biologically targeted agents are ongoing.

Early Stage Breast Cancer

After its approval in the metastatic setting, trastuzumab was evaluated in the adjuvant (post-operative) setting in several large prospective randomized trials that enrolled over 13,000 patients in total. The addition of trastuzumab to chemotherapy led to a significant improvement in DFS (36–58%) and OS (24–59%) [48–52]. As expected, the benefit of trastuzumab is limited to HER2-positive disease [53, 54]. The first regimen evaluated with trastuzumab was doxorubicin, cyclophosphamide followed by paclitaxel, trastuzumab (AC→TH). While effective, this comes at the cost of a 4.1% risk of grade 3/4 heart failure which is attributable to the use of an anthracycline with trastuzumab [55]. A non-anthracycline-based regimen was also evaluated in a trial that enrolled 3,222 women with HER2-amplified early breast cancer and randomly assigned them to receive chemotherapy alone (AC→T;doxorubicin, cyclophosphamide, docetaxel), anthracycline-based chemotherapy plus trastuzumab (AC→TH), or a non-anthracycline based chemotherapy plus trastuzumab (TCH; docetaxel, carboplatin, and trastuzumab). Efficacy analysis at 65 months demonstrated that women receiving either trastuzumab-containing regimen had significantly improved DFS and OS compared to women receiving AC→T. Additionally, there was no statistically significant difference in DFS between the TCH and AC→TH arms. However, there were fivefold greater congestive heart failure events with AC→TH than with TCH [51]. These data support the use of trastuzumab with a non-anthracycline based chemotherapy regimen in the adjuvant treatment of early breast cancer.

Recent evidence suggests that the biology of a tumor may be more important than its size at diagnosis. Two recent studies indicate that sub-centimeter HER2-positive tumors carry a higher risk of recurrence than their HER2-negative counterparts [56, 57]. Moreover, two small, hypothesis-generating retrospective analyses suggest that adjuvant trastuzumab-based therapy may improve outcomes for T1 tumors that are HER2-positive. [58, 59]. Larger, prospective studies to evaluate the use of trastuzumab-based therapy for subcentimeter HER2+ tumors are ongoing.

Locally Advanced Breast Cancer: Neoadjuvant therapy

In locally advanced breast cancer, neoadjuvant (preoperative) chemotherapy has increased rates of breast conserving surgery [60, 61]. Furthermore, neoadjuvant therapy provides an *in vivo* assessment of response to therapy based on pathologic response. For these reasons, neoadjuvant therapy is the standard of care in locally advanced and inflammatory breast cancer, and may be considered in patients with early breast cancer.

Neoadjuvant treatment with trastuzumab and chemotherapy has been evaluated in recently reported Phase III trials. Concurrent administration of trastuzumab and paclitaxel followed by anthracycline-based chemotherapy produced a higher pathologic complete response (pCR) rate than the same chemotherapy alone (65.2% vs 26.3%, p=.016) [62]. Updated safety and efficacy analyses conducted with an additional 22 patients who all received trastuzumab and chemotherapy, demonstrated an improvement in 3-year DFS with the addition of trastuzumab (100% vs 85.3%) [63]. The Neoadjuvant Herceptin (NOAH) trial compared treatment with trastuzumab (for 1 year, starting preoperatively; n=117) with no trastuzumab (n=118), in women with HER2-positive locally advanced or inflammatory breast cancer treated with a neoadjuvant chemotherapy regimen containing doxorubicin, cyclophosphamide, paclitaxel, methotrexate, and fluorouracil. At 3 years, event free survival was significantly improved with the addition of trastuzumab (HR 0.59 [95% CI 0.38–0.90]; p=0.013) [64]. In the German Breast Group/Gynecologic Oncologic Study Group (GeparQuattro) trial, the combination of trastuzumab and anthracycline based chemotherapy (four cycles of epirubicin/cyclophosphamide followed by four cycles of docetaxel with or without capecitabine) in a group of patients with HER2-positive breast cancer produced a greater pCR rate than chemotherapy alone in a reference group of patients with HER2-negative breast cancer (pCR 31.7% vs 15.7% respectively) [65]. TCH has also been investigated in the neoadjuvant setting and has produced pCR rates of 31–43% [66, 67]. Ongoing Phase III clinical trials evaluating neoadjuvant chemotherapy with trastuzumab and other biologic agents, such as lapatinib will further define the role of preoperative administration of HER2 targeted agents [68, 69].

FUTURE DIRECTIONS

Treatment strategies that involve biologic agents with different mechanisms of action are ongoing. These compounds, outlined in Table 1, target several intracellular pathways that contribute to the propagation of HER2-positive breast cancer.

Combination HER2 directed therapy

The combination of lapatinib and trastuzumab has demonstrated synergy in preclinical models [70] and has recently been shown to improve PFS in patients with MBC that had progressed on trastuzumab [71]. In a phase III trial, 296 HER2-positive patients whose disease had progressed on trastuzumab-containing regimens were randomized to receive lapatinib alone or lapatinib with trastuzumab. The median PFS was 12.0 weeks in the lapatinib plus trastuzumab arm and 8.1 weeks in the lapatinib arm (HR 0.73; 95% CI, 0.57 to 0.93; P = .008). The combination of trastuzumab and lapatinib was well tolerated, with fewer serious adverse events than would be expected with a chemotherapy containing regimen [71]. In an updated analysis, the median OS was 14 months for the lapatinib plus trastuzumab arm, compared with 9.5 months for the lapatinib arm (HR=0.74, *P*=.026) [72].

mTOR inhibition

Agents that decrease signaling through the PI3K/Akt/mTOR potentially overcome both trastuzumab and lapatinib resistance. In preclinical models, the mTOR inhibitor, rapamycin, demonstrated synergy with trastuzumab [73]. These compounds, when added to trastuzumab showed clinical activity in Phase I trials of pretreated patients [74]. PI3K inhibitors also impair signaling through this pathway and have shown promise in preclinical studies [75]. The antidiabetic drug, metformin, has been shown to inhibit mTOR and is being evaluated in breast cancer for this reason [76]. Ongoing Phase III studies of mTOR inhibitors in combination with anti-HER2 and chemotherapy will define their role in the treatment of HER2-positive breast cancer.

Angiogenesis Inhibition

Preclinical data demonstrated an interaction between the HER2 and VEGF pathway [77], providing a rationale for combining therapies targeting each. A phase II study of trastuzumab and bevacizumab as first-line therapy for HER2-overexpressing MBC showed that this combination produced an ORR of 48% with acceptable toxicity [78]. Dual tyrosine kinase inhibition with the anti-angiogenesis agent, pazopanib, combined with lapatinib was evaluated in a phase II study of advanced HER2-positive breast cancer. Response rates were improved with combination therapy over lapatinib alone (44% vs 30%, respectively) and a decrease in progressive disease at 12 weeks was observed [79]. Combination VEGF/HER2 blockade is under study in the adjuvant [80] and metastatic settings (with chemotherapy) [81] in two large Phase III trials.

Novel HER2 targeted agents

T-DM1 is an antibody-drug conjugate (ADC) which combines trastuzumab with a potent antimicrotubule agent, DM1, using a stable linker (MCC). This molecule is targeted to HER2-positive cancer cells and is internalized, which may render it less toxic and more effective [82]. A phase II study of T-DM1 in 110 patients with heavily pretreated, HER2-positive MBC demonstrated an ORR of 33% and PFS of 7.3 months. The most common toxicities were nausea, fatigue and thrombocytopenia. No dose limiting cardiotoxicity was observed [83]. Trials comparing first-line treatment with T-DM1 to combination chemotherapy and anti-HER2 agents are ongoing.

Pertuzumab is a monoclonal antibody that targets a different region of the HER2 extracellular domain than trastuzumab. A recent phase II study that evaluated the combination of pertuzumab and trastuzumab demonstrated an ORR of 24.2%, and CBR of 50% of 66 patients whose disease progressed on prior trastuzumab therapy [84].

Neratinib is an oral, pan-ErbB tyrosine kinase inhibitor in development that has shown promise in a Phase II clinical trial [85].

CONCLUSIONS

In the past, HER2 amplification connoted aggressive disease associated with an increased risk of recurrence and death. However, a greater understanding of the molecular mechanisms underlying the pathogenesis of HER2-positive breast cancer has generated treatment options to combat this poor prognosis for many women. By further defining mechanisms of resistance to current treatments and developing new agents to subvert them, the prognosis of HER2-positive breast cancer will continue to be improved.

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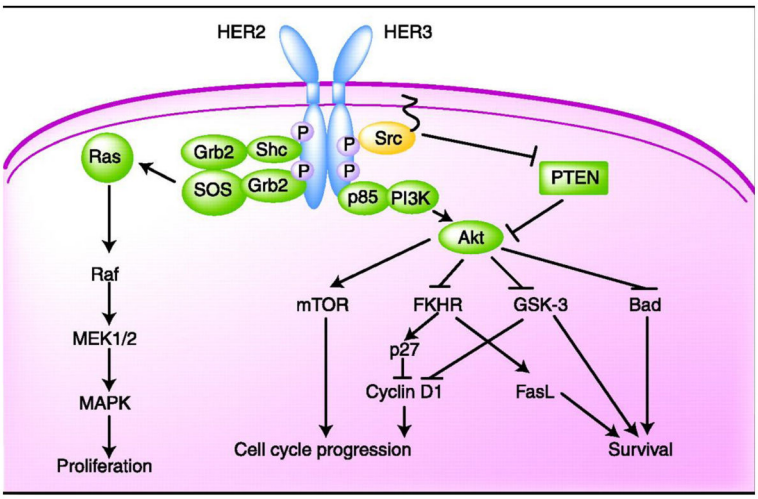

Figure 1. The HER2 Signaling Pathway

Ligand binding induces dimerization, leading to activation of the intracellular tyrosine kinase. On auto- and cross-phosporylation of the receptor complex, key downstream effectors are recruited. This figure illustrates a HER2-HER3 heterodimer, but HER2 can also form homodimers or heterodimerize with other members of the HER2 family. FKHR, forkhead in rhabdomyosarcoma; Grb2, growth factor receptor-bound protein 2; GSK-3, glycogen kinase synthase-3; MAPK, mitogen-activated protein kinase; mTOR, molecular target of rapamycin; PI3K, phospatidyl-inositol 3-kinase; PTEN, phosphatase and tensin homologue deleted on chromosome 10; SOS, son-of-sevenless guanine nucleotide exchange factor.

Table 1

Targeted Therapies for HER2-positive breast cancer

Name	Type	Mechanism of action
Trastuzumab	Receptor antibody	HER2 binding and inhibition
Pertuzumab	Receptor antibody	HER2 dimerization inhibition
Trastuzumab-MCC-DM1	Receptor antibody-toxin conjugate	HER2 binding, maytansine toxin delivery
Lapatinib	Small molecule TKI	Reversible EGFR(HER1) and HER2 inhibition
Neratinib	Small molecule TKI	Irreversible pan-ErbB inhibition
Everolimus	STI	Inhibition of mTOR
Bevacizumab	Antibody	VEGFR ligand inhibition
Pazopanib	Small molecule TKI	VEGFr, c-kit, PDGFr inhibition
Metformin	Biguanide	AMPK activation and mTOR inhibition

AMPK, adenosine monophosphate-activated protein kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mTOR, mammalian target of rapamycin; PDGFr, platelet-derived growth factor receptor; STI, signal transduction inhibitor; TKI, tyrosine kinase inhibitor; VEGFr, vascular endothelial growth factor receptor.