Trastuzumab and Beyond: New Possibilities for the Treatment of HER2-Positive Breast Cancer

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Up to 25% of patients diagnosed with breast cancer have tumors that overexpress HER2. HER2-positive breast cancer is highly proliferative, difficult to treat, and confers a poor prognosis. The advent of the anti-HER2 monoclonal antibody trastuzumab (Herceptin) has markedly altered the clinical course of both early and advanced HER2-driven breast cancer. Despite the use of trastuzumab, however, patients with HER2-positive breast cancer still experience disease progression. Overcoming that resistance to therapy is our next challenge. This review examines the current understanding of HER2 biology, the mechanisms of action of and resistance to trastuzumab, as well as new therapies on the horizon.

Laboratory scientists have confirmed what oncologists have known for years—breast cancer is a heterogeneous disease with multiple potential biologic abnormalities driving tumor growth and response to therapy. One of the most clearly defined biologic abnormalities with clinical relevance is HER2 overexpression. The development of trastuzumab (Herceptin), an amazingly active HER2-targeted drug with effectiveness in both the metastatic and adjuvant settings, has altered the course of HER2-positive breast cancer. Our challenge now is to better understand the heterogeneity of HER2-driven breast cancer, the mechanism of action of trastuzumab, and the mechanisms of resistance to HER2-targeted therapy, all of which will enable us to develop new therapies to treat patients with HER2-positive breast cancer.

HER2 Biology
HER2 is a tyrosine kinase receptor protein expressed on the surface of epithelial cells in a variety of normal tissues including the breast.[1] It is a member of a family of tyrosine kinase receptors known as the ErbB tyrosine kinase receptors. The family comprises four homologous receptors: HER1 (ErbB1, the epidermal growth factor receptor, or EGFR), HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4). The biology of these receptors has been extensively reviewed by several authors, and the reader is referred to their papers for detailed information.[2-4] In general, each receptor protein is composed of an extracellular binding domain, a transmembrane lipophilic segment and an intracellular tyrosine kinase domain with a regulatory carboxyl terminal segment. While HER1, HER2, and HER4 are all intact receptors, HER3 has an inactive tyrosine kinase domain. A soluble ligand has been identified for all members of the HER family except for HER2.

All of these receptors are activated by dimerization, either with an identical receptor (homodimerization) or with a different receptor of the same family (heterodimerization). Normally, HER2 activation occurs when a ligand binds to another HER family member heterodimerized with HER2. Ligand-binding activates the intracellular tyrosine kinase domain, which results in activation of downstream targets through phosphorylation. As illustrated in Figure 1, these targets include pathways involved in cell proliferation (via Ras/Raf/MAP-kinase) and survival (via PI3-Kinase/Akt).
In approximately 25% of breast cancers, up to 100-fold overexpression of the HER2 receptor occurs, primarily due to excess gene copy number.\[5,6\] In these HER2-overexpressing breast cancers, increased receptor density on the cellular surface probably results in HER2 homodimer formation leading to autoactivation, unregulated proliferation, escape from apoptosis, and transformation from benign to malignant cells.

Clinical Implications of HER2-Positive Breast Cancer

Although much is made of the breast cancer "intrinsic" subtypes identified by comprehensive gene-expression profiling,\[7-11\] increased HER2 expression is seen in at least two of the intrinsic subtypes. One, the HER2-positive/ER-negative subtype, is characterized by high expression of HER2-related genes and low expression of estrogen receptor-related genes. High HER2 expression can also be seen in the luminal (ER-positive) subtypes, although less frequently. It remains unclear whether these two groups, HER2-positive/hormone receptor-negative and HER2-positive/hormone receptor-positive, respond differently to HER2-directed therapy. Regardless of subtype, HER2 overexpression confers strong proliferative and survival impulses and is associated with larger tumors, higher likelihood of nodal involvement, high histologic tumor grade, aneuploidy, and poor outcome.\[12-16\]

HER2-Targeted Therapy With Trastuzumab

Trastuzumab—a humanized mouse monoclonal antibody targeted to an epitope on the extracellular domain of HER2[17]—was the first US Food and Drug Administration (FDA)-approved drug to target the HER2 cell-signaling pathway. Clear evidence of the drug's clinical efficacy was first established in a phase III trial, in which previously untreated metastatic breast cancer patients with HER2-overexpressing tumors (2+ or 3+ by immunohistochemical [IHC] staining) were treated with standard chemotherapy with or without trastuzumab.[18] Standard chemotherapy was defined as an anthracycline plus cyclophosphamide (AC) for chemotherapy-naive patients, or paclitaxel given once
every 3 weeks for patients who had received adjuvant anthracycline. Chemotherapy was given simultaneously with trastuzumab, which was administered weekly until disease progression. The addition of trastuzumab to chemotherapy resulted in a longer time to progression, a higher rate of objective response, longer survival and a lower rate of death at 1 year compared to chemotherapy alone.[18] In addition, the duration of response was increased from 6 to 9 months, which speaks to both the effectiveness of the drug and the inevitability of acquired resistance. In general, the combination of chemotherapy plus trastuzumab was well tolerated. However, a surprisingly high level of cardiac-dysfunction (27%) was seen in the AC-plus-trastuzumab arm, compared to 8% in the AC-alone arm and 13% in the paclitaxel-plus-trastuzumab arm. This had not been predicted by preclinical or early clinical studies. For this reason, avoidance of cardio-toxicity is a major theme of research aimed at improving HER2-directed therapy.

Subsequent work has revealed that normal cardiac myocyte function depends upon HER2 expression.[19] Interestingly, trastuzumab-related cardiotoxicity appears to differ from anthracycline-induced cardiotoxicity. Anthracycline-mediated cardiac damage is dose-related, infrequent, reversible, and associated with pathologic changes in the myocardial muscle, whereas trastuzumab cardiotoxicity may be reversible, not dose-related, and not associated with specific pathologic changes in the myocardium.[20,21]

Single-Agent Trastuzumab

Trastuzumab was also found to be effective when used as a single agent in metastatic breast cancer patients with HER2-overexpressing tumors (2+ or 3+ by IHC),[22] demonstrating a 26% objective response rate in the first line setting and 12% in pretreated patients.[23] During these early years of HER2 targeting, the testing methods for HER2 expression improved, and the ambiguity of moderate (2+) IHC staining became clearer.[24] An even greater clinical impact of the drug was seen when more stringent HER2 criteria were used; for example, when the first-line single-agent data were stratified by HER2 categories, the objective response rate was 35% in 3+ HER2 tumors vs 0% in 2+ tumors, and 34% in fluorescence in situ hybridization (FISH)-positive tumors (gene-amplified) vs 7% in FISH-negative tumors. These observations highlight the fact that accurate HER2 testing is crucial and that only patients with HER2-positivity defined as 3+ overexpression by IHC or gene amplification (FISH-positive) benefit from trastuzumab therapy. Since these landmark trials, several other investigators have combined trastuzumab with various chemotherapy regimens in the metastatic setting, including vinorelbine, docetaxel (Taxotere), paclitaxel plus carboplatin, and even pelygated liposomal doxorubicin (Doxil).[25-27] In all these trials, the combination of trastuzumab plus chemotherapy was more effective than chemotherapy alone. The cardiac toxicity (defined as asymptomatic left-ventricular ejection fraction decline or symptomatic congestive heart failure) from trastuzumab plus chemotherapy ranged from 2% to 17%.

Nonmetastatic Settings

The benefit of trastuzumab in HER2-overexpressing breast cancer patients outside of the metastatic setting was first suggested in a randomized neoadjuvant trial of paclitaxel followed by FEC75 (fluorouracil, epirubicin [Ellence] at 75mg/m², and cyclophosphamide) with or without trastuzumab. The addition of trastuzumab more than doubled the pathologic complete response rate (67% vs 25%) when compared to chemotherapy alone.[28] However, resistance exists even in the most active trastuzumab-containing regimens given to the most treatment-naive patients; 3 of 23 patients had residual nodal disease even after 24 weeks of combined chemobiotherapy. The proof of effectiveness in the adjuvant setting came with the reports from the joint analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B31 and North Central Cancer Treatment Group (NCCTG) N9831 trials,[29,30] the Breast Cancer International Research Group (BCIRG) 006 trial,[31,32] and the Herceptin Adjuvant (HERA) trials.[29,30] The B31/N9831 analysis and BCIRG 006 trial revealed that 1 year of trastuzumab added to AC followed by a taxane (AC-TH) is remarkably effective, producing an approximately 10% absolute improvement in disease-free survival even by 3 years; this benefit was seen equally across all clinically identifiable subgroups. BCIRG 006 found a slightly lower but statistically similar benefit with a nonanthracycline regimen (docetaxel, carboplatin, and trastuzumab, or TCH), which improved disease-free survival by 3%. HERA, in which HER2-positive patients received 1 year of adjuvant trastuzumab therapy vs observation after at least four cycles of neoadjuvant or adjuvant chemotherapy, demonstrated an absolute benefit of 9% at 2 years.

By avoiding concurrent anthracycline/trastuzumab therapy, as in the TCH arm of BCIRG 006, or giving the trastuzumab after chemotherapy, as in HERA, the incidence of clinical cardiotoxicity improves (approximately 2% vs 4%), but at the risk of potentially poorer efficacy. In all of these
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studies, 10% to 15% of patients relapsed in spite of highly effective regimens that involved more than 1 year of infusional trastuzumab therapy and a risk of clinical cardiotoxicity.

A substudy within BCIRG 006 suggests that the benefit of an anthracycline-based regimen such as AC-TH over a non-anthracycline-based regimen such as TCH may be primarily limited to HER2-positive tumors that also demonstrate topoisomerase II-alpha gene amplification. This intriguing but preliminary finding is consistent with earlier observations regarding topoisomerase II-alpha gene amplification and anthracycline sensitivity[33-35] and may identify a group in which the less cardiotoxic trastuzumab regimen (TCH) may be used without loss of clinical efficacy. None of the adjuvant trastuzumab trials identified a subset of patients more or less likely to benefit from trastuzumab therapy. Thus, unlike the emerging evidence that the benefit of chemotherapy, in part, can be predicted by hormone-receptor status,[36] we do not yet have a predictive factor for trastuzumab efficacy in patients with HER2-positive breast cancer.

Trastuzumab Mechanisms of Action

Although the efficacy of trastuzumab in a variety of clinical settings is well established, the biologic explanation for its efficacy is not so well defined. Several theories have been proposed to explain the mechanism of trastuzumab action, and scientific data support each theory (Table 1).

<table>
<thead>
<tr>
<th>Proposed Mechanisms of Action</th>
<th>Observed In Vitro</th>
<th>Observed In Vivo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Downregulation of HER2 protein[37-41]</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>G1 cell-cycle arrest leading to growth inhibition[42-44]</td>
<td>Yes</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Apoptosis[41,42,46]</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Antibody-dependent cellular cytotoxicity[17,38,40,51]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Antiangiogenesis[48,49]</td>
<td>Yes</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Inhibition of HER2 extracellular domain cleavage[52]</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Based on preclinical data, the mechanism of the antiproliferative and proapoptotic actions of trastuzumab was presumed to be downregulation of HER2-receptor expression; however, this in vitro observation has not been confirmed in vivo.[37-41] As mentioned, HER2 activates multiple cell-signaling proliferation and survival pathways, including the MAPK and PI3K/Akt pathways. Trastuzumab binding to HER2 decreases signaling from these pathways, causing G1 arrest, growth inhibition, and apoptosis.[41-47]

In addition to its effect on cell-signaling, trastuzumab induces antibody-dependent cellular cytotoxicity against HER2-overexpressing tumor cells and appears to have antiangiogenic properties.[17,38,40,48-51] Finally, trastuzumab blocks the proteolytic cleavage of the extracellular domain of HER2, a process that produces p95—a truncated, constitutively activated, membrane-bound version of HER2.[52] How much each of these mechanisms contributes to trastuzumab's clinical effects is not yet clear.

Trastuzumab Resistance

In theory, interference with any of these proposed mechanisms of action could lead to trastuzumab resistance. Clinically, we know that de novo trastuzumab resistance exists, since in the first-line single-agent setting, only one-third of patients with metastatic HER2-overexpressing breast cancer respond to the drug.[22] We also know that acquired resistance occurs, since the majority of patients with metastatic HER2-overexpressing breast cancer who initially respond to trastuzumab have disease progression within 12 months of starting therapy.[18,22] As we become more knowledgeable about the mechanisms of action and the mechanisms of resistance to trastuzumab, it
becomes obvious that the oncologist and the cancer are continually adapting to changes in each other. For this reason, each of the mechanisms described here serves as a potential target for therapeutic development.

**Bypass Mechanisms**

There are numerous ways that trastuzumab's normal action could be subverted (Table 2). For several of these strategies, targeted agents are already in clinical trials (Table 3).

**Table 2**

**Proposed Mechanisms of Trastuzumab Resistance**

<table>
<thead>
<tr>
<th>Mechanisms of Trastuzumab Resistance</th>
<th>Possible Therapeutic Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation of signaling thru HER1 via HER1 ligand[54,55]</td>
<td>Blockade of HER1 and HER2 or blockade of HER1/HER2 dimerization</td>
</tr>
<tr>
<td>Mutation of HER2 to prevent trastuzumab binding</td>
<td>?</td>
</tr>
<tr>
<td>Increase the degradation of HER2[59]</td>
<td>Inhibit HSP90, a protein that prevents proteasomal degradation of HER2</td>
</tr>
<tr>
<td>Blockage of trastuzumab binding of HER2 by increased cell surface mucin[53]</td>
<td>Decreasing cell surface mucin</td>
</tr>
<tr>
<td>Activation of IGF-1R signaling thru PI3K/Akt pathway[62,63]</td>
<td>Inhibition of IGF-1R or blockade of IGF-1R/HER2 heterodimerization</td>
</tr>
<tr>
<td>Loss of PTEN[45]</td>
<td>Replacement of PTEN function</td>
</tr>
<tr>
<td>Downregulation of p27kip[61]</td>
<td>Inhibition of proteosome-dependent degradation</td>
</tr>
</tbody>
</table>

*IGF-1R = insulin-like growth factor 1 receptor; PI3K = phosphatidylinositol-3-kinase; PTEN = phosphate and tensin homolog.*
<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Compound</th>
<th>Clinical Trial Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER1/HER2 inhibitor</td>
<td>Lapatinib</td>
<td>Phase I, II, III, IV</td>
</tr>
<tr>
<td>Pan HER inhibitor</td>
<td>Canertinib (CI-1033)</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>BMS-599626</td>
<td>Phase I</td>
</tr>
<tr>
<td>HER1/HER2/VEGFR inhibitor</td>
<td>AEE788</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>EXEL 7647/EXEL 0999</td>
<td>Phase I</td>
</tr>
<tr>
<td>HER2 dimerization inhibitor</td>
<td>Pertuzumab (2C4)</td>
<td>Phase II</td>
</tr>
<tr>
<td>HSP90 inhibitor</td>
<td>Tanespimycin (17AAG, KOS-953)</td>
<td>Phase I, II</td>
</tr>
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<td></td>
<td>Alvespimycin (KOS1022)</td>
<td>Phase I</td>
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<td></td>
<td>IPI-504</td>
<td>Phase I</td>
</tr>
<tr>
<td>IGF-1R small-molecule inhibitors</td>
<td>NVP-ADW742</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>Insm-18</td>
<td>Phase I</td>
</tr>
<tr>
<td>Anti-IGF-1R antibodies</td>
<td>EM164</td>
<td>Phase I</td>
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<td></td>
<td>CP-751-871</td>
<td>Phase I, II</td>
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<tr>
<td></td>
<td>IMC-A12</td>
<td>Phase I</td>
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<td>HDAC inhibitors (short-chain fatty acids)</td>
<td>Butyrate</td>
<td>Phase I, II</td>
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<tr>
<td></td>
<td>Valproic acid</td>
<td>Phase I, II</td>
</tr>
<tr>
<td>HDAC inhibitors (hydroxylamine acids)</td>
<td>PXD101</td>
<td>Phase I, II</td>
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<tr>
<td></td>
<td>SAHA</td>
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<tr>
<td></td>
<td>LBH589</td>
<td>Phase I</td>
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<tr>
<td></td>
<td>NVP-LAQ824</td>
<td>Phase I</td>
</tr>
<tr>
<td>HDAC inhibitors (cyclic tetrapeptides)</td>
<td>Depsipeptide (FR901228, NSC 630176)</td>
<td>Phase I, II</td>
</tr>
<tr>
<td>HDAC inhibitors (benzamides)</td>
<td>CI-994 (acetyldinmaleine)</td>
<td>Phase I, II</td>
</tr>
<tr>
<td></td>
<td>MS-275</td>
<td>Phase I, II</td>
</tr>
<tr>
<td>DNA methylation inhibitor</td>
<td>5-Azacytidine</td>
<td>Phase I, II, III</td>
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<tr>
<td>(nucleoside analogs)</td>
<td>Decitabine</td>
<td>Phase I, II, III</td>
</tr>
<tr>
<td></td>
<td>(5-aza-2’-deoxycytidine)</td>
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<tr>
<td>DNA methylation inhibitor</td>
<td>Hydralazine</td>
<td>Phase I</td>
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<tr>
<td>(nonnucleoside analogs)</td>
<td>MG98</td>
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<tr>
<td>PI3K inhibitors</td>
<td>SF1126</td>
<td>Phase I</td>
</tr>
<tr>
<td>Akt inhibitors</td>
<td>Perifosine</td>
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<tr>
<td>mTOR inhibitors</td>
<td>RAD001</td>
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<td></td>
<td>CCI-779</td>
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<td></td>
<td>Rapamycin</td>
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<td>AP-23573</td>
<td>Phase II</td>
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<tr>
<td>Proteasome inhibitors</td>
<td>Bortezomib</td>
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</tr>
<tr>
<td></td>
<td>NPI-0052</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

HDAC = histone deacetylase; mTOR = mammalian target of rapamycin; IGF = insulin-like growth factor; PI3K = phosphatidylinositol-3-kinase; SAHA = suberoylanilide hydroxamic acid; VEGFR = vascular endothelial growth factor receptor.
We will begin outside the membrane. Trastuzumab binds to the extracellular portion of HER2 near the membrane. HER2 heterodimerization with other HER family members such as HER1 or HER3 can still occur despite the administration of trastuzumab.[53-55] The importance of this cross-talk in preventing trastuzumab effectiveness has been demonstrated in HER2-overexpressing cell lines, in which inhibition of HER2 signaling is inversely related to HER1 expression,[55] suggesting that activation of lateral signaling pathways can bypass HER2 blockade. This potential role for HER1 in trastuzumab resistance presents therapeutic opportunities to target both receptors by HER1/HER2 inhibitors such as lapatinib (Tykerb), pan-HER inhibitors such as canertinib (CI-1033), and HER2 antibodies that block the dimerization site such as pertuzumab (2C4, Omnitarg).

The clinical efficacy of combined HER1/HER2 inhibition by lapatinib in trastuzumab-resistant HER2-positive breast cancer (discussed further below) is a testament to the importance of this mechanism in acquired trastuzumab resistance. The role of HER1 in primary resistance is less clear. In one retrospective study, HER1 expression in the primary breast cancers of women subsequently treated with trastuzumab did not correlate with response,[56] and in a randomized phase I/II trial, addition of the HER1 kinase inhibitor gefitinib (Iressa) to trastuzumab in the trastuzumab-naive metastatic setting showed no benefit.[57]

Alterations in HER2-Trastuzumab Interactions

Another obvious way to ameliorate trastuzumab's action would be to prevent trastuzumab binding by mutating HER2; such HER2 mutations have been reported in lung cancer.[58] De novo extracellular domain mutations in breast cancer are infrequent, but it is possible that such mutations may be acquired under the selective pressure of ongoing trastuzumab therapy. Alternatively, the cell could increase the degradation of HER2 by inhibiting Hsp90, a chaperone protein that normally functions to prevent proteasomal degradation of HER2.[59] Preliminary but interesting data from a phase I dose escalation trial combining the Hsp90 inhibitor 17-AAG with trastuzumab revealed that all five cases of tumor regression occurred among the 17 patients with HER2-positive, trastuzumab-resistant breast cancer, supporting the phase II study that is underway.[60] Competition at the cell surface is another potential means to block trastuzumab binding. In one cell line from a patient with primary trastuzumab-resistant disease, increased expression of membrane-associated MUC4 appeared to result in decreased trastuzumab binding.[53]

Alternative Receptor Activation

In addition to alterations in HER2-trastuzumab interactions and bypass mechanisms, abrogation of trastuzumab's effectiveness can occur by activation of alternative cell surface receptors such as insulin-like growth factor receptor (IGF-1R) that activate the PI3K/Akt pathway.[45,61-65] In support of this mechanism of resistance, high IGF-1R expression in pretreatment tumor samples from women later treated with trastuzumab was associated with early progression.[56] These data strengthen the clinical rationale for combination IGF-1R/HER2 targeting strategies that have been proposed based on synergy in cell line studies.[66] Anti-IGF-1R monoclonal antibodies such as IMC-A12 and small-molecule inhibitors such as insm-18 are currently in clinical testing (Table 3).

Intracellular Mechanisms

Moving our attention to the intracellular setting, HER2 kinase domain mutations resulting in the constitutive activation of HER2/HER1 heterodimers have been detected in lung cancer. This way, receptor-antibody interaction is not disrupted, but HER2 signaling is altered. While few data yet exist in breast cancer, in lung cancer these HER2 kinase domain mutations confer resistance to HER1-directed small-molecule kinase inhibitors.[67]

In addition to activation by alternative receptors, the PI3K/Akt pathway may be activated by other non-HER2-dependent mechanisms, such as the loss of PTEN.[45,65] PTEN deficiency caused by a variety of mechanisms including epigenetic silencing is seen in approximately 40% of breast cancers. In a small study of 47 breast cancer patients treated with trastuzumab plus taxane, PTEN-deficient tumors by IHC had significantly lower response rates than those with normal expression.[45] Compounds like histone deacetylase (HDAC) inhibitors or DNA methylation inhibitors that can reverse epigenetic silencing phenomenon in vitro are in various stages of clinical development (Table 3) and may play a role in the future.[68] For example, vorinostat (Zolinza), an HDAC inhibitor, is being studied in a phase I/II study combined with trastuzumab therapy for treating patients with HER2-overexpressing breast cancer.

Directly inhibiting either PI3K or Akt could also decrease signaling through the PKB/AKT pathway. Several compounds are in development along these lines and starting to enter the clinic (Table 3).[69] One compound—an Akt inhibitor (perifosine)—has also been paired with trastuzumab in a phase I clinical trial targeting patients with HER2-overexpressing breast cancer. Through its role as a
downstream effector of Akt signaling, mTOR (mammalian target of rapamycin) is also a potential therapeutic target. Several mTOR inhibitors are in clinical testing (Table 3), and at least one, RAD001, is in phase I/II trials combined with trastuzumab in patients who have already had disease progression on trastuzumab.

Proteasome inhibitors can decrease the degradation of p27^Kip1, thereby increasing signaling thru the RAS/MAPK pathway.[61] The most developed proteasome inhibitor is bortezomib (Velcade), which is currently being evaluated in a phase II trial of the agent given concurrently with trastuzumab in patients with HER2-overexpressing breast cancer.

HER2 Vaccine

The majority of approaches to treating breast cancer focus on exogenous chemotherapeutics that are directly toxic to the tumor. An alternative approach, however, is to stimulate the innate immune system to attack and eliminate the tumor cells. In breast cancer, several research groups are trying to develop a vaccine targeting the HER2 protein. The theory behind such an approach is that stimulation of the patient’s own immune system to target the HER2 protein should lead to the death of cells expressing the protein (ie, tumor cells). Preliminary in vivo data indicate that epitope-specific immune responses can be generated by vaccinating patients with either the entire HER2 protein, or select peptides derived from the receptor that have been shown to be immunogenic in animal models.[70-72] Preliminary studies suggest that patients with node-positive, HER2-overexpressing breast cancer treated with HER2-targeted vaccine may have a lower rate of recurrence compared to patients who weren’t vaccinated.[73]

Lapatinib

Given recently reported evidence of clinical efficacy in a randomized phase III clinical trial, we will discuss lapatinib separately. Lapatinib is a small-molecule inhibitor that competes with ATP for binding sites on the intracellular portion of both HER1 and HER2, and reversibly inhibits their function. In vitro, lapatinib triggers apoptosis in HER2-overexpressing breast cancer cell lines, while the combination of lapatinib and trastuzumab induces apoptosis at an even higher level than either agent alone.[74] Like trastuzumab, lapatinib is believed to induce apoptosis by modulating the PI3K/Akt pathway.[74]

Clinical Findings

The first data supporting lapatinib efficacy in the clinic came from a phase I dose-escalation study in which patients with HER1- and/or HER2-overexpressing metastatic cancer (any solid tumor) were treated with lapatinib.[75] Even in this heavily pretreated population, lapatinib treatment resulted in partial responses in 4 of 59 patients (7%) and stable disease in 24 of 59 (41%). Of note, clinical responses correlated with higher pretreatment levels of HER2 expression but not pretreatment HER1 expression.[76]

Several phase II trials with lapatinib are in various stages of completion with interim data analysis presented at recent American Society of Clinical Oncology (ASCO) meetings. One of the first of these studies enrolled patients with trastuzumab-refractory metastatic breast cancer, in which 8 of 36 patients (22%) showed clinical benefit from treatment (partial response plus stable disease rates) with an acceptable toxicity profile.[77] These results were supported by additional data from the EGF103009 trial, in which all patients had relapsed/refractory inflammatory breast cancer with either HER2 or HER1 overexpression, and 8 of 11 patients (72%) with HER2 overexpression had a clinical response (complete plus partial response). There were no responders among HER1-positive patients.[78] These data suggest that clinical response to single-agent lapatinib is primarily seen in HER2 overexpressors.

The interim analysis for EGF100151, a large phase III study comparing capecitabine (Xeloda) to capecitabine plus lapatinib in patients with pretreated HER2-overexpressing locally advanced or metastatic breast cancer, was presented at the 2006 ASCO meeting. The trial was stopped prematurely when the median time to progression (the primary endpoint: 37 vs 20 months), median progression-free survival, and response rates all favored combination therapy (capecitabine/lapatinib) over capecitabine alone.[79] Given the synergy noted in preclinical studies, several proposed or ongoing trials in the metastatic, adjuvant, and neoadjuvant settings will examine the combination of lapatinib and trastuzumab in patients with HER2-overexpressing breast cancer.

Conclusions

Although all the compounds mentioned above theoretically may be used to treat trastuzumab-resistant breast cancers, each has its limitations. Many are barely starting clinical development, and both de novo and acquired resistance to the most clinically developed compound, lapatinib, has already been demonstrated. For lapatinib, breast cancer cells with acquired resistance...
appear to become less dependent on HER2 signaling for cell survival and more dependent on estrogen-receptor (ER) signaling in conjunction with HER2 signaling.[80] This observation raises the question of whether serial examination of tumor material throughout the course of a patient's treatment would reveal the evolution of the tumor's biology from HER2 dependence to codependence on HER2 and ER, even if the initial tumor was hormone receptor-negative. Given that we seldom rebiopsy tumors after the initial diagnosis has been made, this and similar questions regarding tumor evolution during therapy remain unanswered.

New options for HER2-positive breast cancer are coming. With them, we will soon have a whole new set of questions regarding timing and optimal combination of these targeted agents, which is a nice problem to have.

Disclosures:
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References:


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