The HER2 World: Better Treatment Selection for Better Outcome

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Understanding the mechanisms of trastuzumab efficacy and resistance is a step toward optimizing treatment outcome in HER2-positive breast carcinoma patients. Preclinical studies have indicated different trastuzumab antitumor mechanisms, that is, cytostatic inhibition of tumor proliferation, antibody-dependent cell cytotoxicity, and inhibition of HER2-mediated DNA repair. Clinical studies point to the clinical setting dependence of these mechanisms, with antibody-dependent cell cytotoxicity predominating when trastuzumab is used as monotherapy in neoadjuvant and metastatic settings, whereas inhibition of DNA repair predominates in neoadjuvant and adjuvant settings involving concomitant trastuzumab and chemotherapy; in sequential protocols, the antibody appears to act primarily through cytostatic activity by inhibiting HER2-mediated cell proliferation. Because the mechanisms of resistance to trastuzumab likely depend directly on those of its antitumor activity, resistance mechanisms must also be considered with respect to the different clinical settings. Moreover, the response to this reagent should be assessed according to its ability to induce tumor cytotoxic or cytostatic activity.

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HER2 is a 185-kD transmembrane receptor in the HER family of receptor tyrosine kinases, which also includes HER1, HER3, and HER4. Heterodimerization of HER2 with the three other HER receptors is induced by specific ligands, whereas only HER2 can dimerize in the absence of a ligand and, once activated, is able to mediate prosurvival signals mainly through activation of the PI3K pathway.

HER2 gene amplification is rare except in breast cancer, in which both amplification of the gene and HER2 protein overexpression occur in approximately the same proportion of cases (20%–30%). Various clinical studies have shown that women with HER2-positive tumors have a poorer prognosis than those with HER2-negative tumors (1). Differential levels of HER2 expression in HER2-overexpressing breast carcinomas vs normal cells, together with the demonstration of a key role for HER2 in tumor progression, make HER2 an ideal target for specific therapeutic approaches. Because of the survival benefit of trastuzumab, a recombinant humanized monoclonal antibody directed to the extracellular domain of the HER2 protein, this reagent was approved in 1998 by the US Food Drug and Administration for treatment of women with HER2-positive metastatic breast cancer and, in 2006, approved for patients with early breast cancer. Although results thus far demonstrate the clinical benefit of trastuzumab, the therapy appears to be effective in only about 50% of patients with HER2-positive breast carcinoma. An understanding of the different mechanisms whereby trastuzumab exerts its therapeutic effect in different clinical settings is crucial in identifying the related resistance mechanisms to this treatment. Such information is of utmost importance in identifying patients likely to benefit from this treatment and in designing strategies to overcome the resistance.

Five potential mechanisms of trastuzumab action have emerged from preclinical studies: 1) antibody-dependent cellular cytotoxicity (ADCC); 2) inhibition of signal transduction and cell cycle arrest; 3) inhibition of HER2 extracellular domain proteolytic cleavage and consequent inhibition of activated p95–truncated HER2 receptor; 4) inhibition of tumor angiogenesis; and 5) inhibition of DNA repair [reviewed in (2)]. Three of these activities, inhibition of HER2 signaling, extracellular domain shedding, and tumor angiogenesis, exert principally a cytostatic action, whereas the other two, ADCC and inhibition of DNA repair, have a cytotoxic effect (Figure 1).

All of the emerging data from clinical studies suggest that trastuzumab can act through multiple mechanisms in patients, according to stage of disease and treatment protocol.

Trastuzumab Mechanisms of Action in Patients

Trastuzumab in Monotherapy

Only a few studies have considered the treatment with trastuzumab alone. A small pilot study of 18 HER2-positive patients with trastuzumab as monotherapy in a neoadjuvant setting indicated a cytotoxic response rate of 50% as evaluated with the RECIST (Response Evaluation Criteria In Solid Tumors) system. Patients who achieved complete or partial remission presented tumors with a higher in situ infiltration of leukocytes and peripheral blood mononuclear cells with a greater ability to mediate in vitro ADCC, suggesting that this mechanism of action is highly active (3,4). The ability of trastuzumab to reduce tumor mass when used as monotherapy in a clinical trial of 111 metastatic patients supports the involvement of ADCC in this clinical setting (5).
neoadjuvant-treated patients (25% vs 50%, respectively) might rest in the compromised immune status due to chemotherapy. Nonetheless, trastuzumab inhibition of tumor growth by blocking HER2-mediated signaling, formation of active truncated p95 receptor, and/or release of angiogenic factors might also contribute in inducing a cytostatic action on tumor cells still present upon immune cell-mediated killing.

Trastuzumab in Combination With Chemotherapy

Trastuzumab given concomitantly with chemotherapy in a neoadjuvant setting reportedly leads to a high percent of complete pathological response, indicating a synergistic effect between the two therapies (6–11). Only a trastuzumab-mediated block in the DNA repair by nuclear HER2 can convincingly explain the synergy between trastuzumab and chemotherapy in this setting. Indeed, chemotherapy induces DNA damage, and cells respond by activating genes involved in cell cycle arrest, DNA repair, and apoptosis. Signal transduction pathways, including those mediated by HER2, are important for the induction of repair genes; inhibition of HER2 signaling by trastuzumab could impair this process, increasing the cytotoxic activity of the drug. Considering that a low proliferation rate is associated with resistance rather than sensitivity to chemotherapy, it is very unlikely that trastuzumab-induced inhibition of tumor cell growth is involved in the synergy between the two treatments. ADCC also probably does not explain this synergy because most drugs have a potent inhibitory effect on the immune system. DNA repair inhibition mediated by trastuzumab could also explain why concomitant trastuzumab plus chemotherapy adjuvant protocols are more active and with a longer-lasting effect than the sequential protocol (12,13).

In the sequential protocol, the activity of trastuzumab appears to decrease during time of observation, strongly suggesting a cytostatic activity associated with antibody-mediated inhibition of proliferation. Indeed, at the end of treatment with trastuzumab, micrometastatic cells begin to grow again. In this setting, ADCC is probably minimally active because chemotherapy delivered before trastuzumab heavily impairs the lymphoid system, including cells mediating ADCC. Moreover, if trastuzumab activated killing by ADCC, a long-lasting effect would be expected.

Clinical trials in metastatic patients indicate that tumors maintain trastuzumab sensitivity even during progression under trastuzumab treatment (14,15). However, despite the effectiveness of trastuzumab in increasing overall survival, few metastatic patients, if any, are actually cured of the disease. Thus, trastuzumab appears to exert principally a cytostatic activity in these patients, although, ADCC and DNA repair inhibition might also play some role depending on the drugs combined and the patients’ immune status, respectively.

Resistance to Trastuzumab

Clinical data indicate that trastuzumab acts through multiple mechanisms in patients, pointing to an analogous multiplicity in the mechanisms of resistance to the treatment, which are frequently directly dependent on the activity (Table 1).

Table 1. Mechanisms of trastuzumab action and corresponding resistance or response evaluation methods*

<table>
<thead>
<tr>
<th>Trastuzumab activity</th>
<th>ADCC</th>
<th>DNA repair inhibition</th>
<th>Cell growth inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure of response</td>
<td>RECIST</td>
<td>RECIST</td>
<td>DFS/OS evaluation</td>
</tr>
<tr>
<td>Mechanism of resistance</td>
<td>Potential low NK activity</td>
<td>Tumor resistance to chemotherapeutic drug</td>
<td>Alteration of molecules downstream HER2</td>
</tr>
<tr>
<td></td>
<td>Tumor expression of NK suppressors</td>
<td>No HER2-mediated DNA repair</td>
<td>High expression of truncated p95HER2</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Increased signaling from other receptors</td>
</tr>
</tbody>
</table>

* ADCC = antibody-dependent cell cytotoxicity; DFS = disease-free survival; NK = natural killer; OS = overall survival; RECIST = Response Evaluation Criteria In Solid Tumors.
The resistance to trastuzumab-induced ADCC must take into consideration mechanisms associated with effector cells and with tumor cells. Factors in the patient’s immune system, such as reduced natural killer (NK) cell numbers and/or activity as well as the presence of NK genotypic variants with low affinity for trastuzumab, have been found to reduce the ADCC response to trastuzumab (2). Furthermore, production of molecules such as transforming growth factor (TGF)-β and interleukin-10, which inhibit NK killing through the perforin/granzyme system, as well as high-level production of major histocompatibility complex molecules by tumor cells might also reduce or block ADCC for trastuzumab. None of these factors has been well studied in vivo, and their relevance awaits further investigation.

Because the synergistic antitumor activity of trastuzumab in combination with chemotherapy implicates HER2 in DNA repair mechanisms, and thus presumably depends on the potency of drugs in inducing DNA damage, identification of drugs with cytotoxic activities that can better synergize with trastuzumab represents a potential avenue to optimal therapeutic effects.

When cytostatic activity through the blockade of tumor cell proliferation is the prevalent trastuzumab mechanism, alteration of molecules downstream in the HER2 signaling pathway might bypass the membrane receptor and promote tumor proliferation no longer related to its activation. In this context, in vitro studies have identified alterations in the HER2 signaling pathway, such as PI3K mutation, PTEN knockdown, and p27 decreased levels (16–18). Furthermore, overproduction of TGF-α and heparin-binding-epidermal growth factor or truncated HER2 receptor has been associated with resistance to trastuzumab (19,20). Resistance may also occur through increased signaling from other HER family receptors (eg, HER3) and from insulin-like growth factor receptor (21,22), suggesting the potential of future therapies that couple trastuzumab with agents that inhibit additional pathways. However, to date, none of these markers has proven sufficiently reliable in vivo to identify patients likely to be trastuzumab resistant, possibly due to the inappropriate use of response evaluation criteria. Indeed, only disease progression is indicative of trastuzumab ineffectiveness in blocking tumor growth (Table 1).

Other Anti-HER2–Targeted Therapies

Another inhibitor of HER2-associated proliferation is lapatinib, a small tyrosine kinase inhibitor molecule. The advantage of the small molecule is the higher possibility of diffusion in the tumor mass; the disadvantage is the lack of alternative mechanisms of action, such as ADCC, specifically associated only with antibody reagents. However, if HER2 activation is prerequisite for its translocation to the nucleus where it exerts its DNA repair activity, this tyrosine kinase inhibitor could synergize better than trastuzumab with chemotherapeutic drugs in inducing tumor cytotoxicity. The combination of lapatinib and trastuzumab has been shown to be active in patients who progressed under trastuzumab therapy; the different mechanisms of trastuzumab activity, together with the high diffusion of lapatinib, likely explain the favorable effect of this protocol (15). Synergistic effects between pertuzumab and trastuzumab, each directed against different HER2 epitopes, have been reported (23), consistent with both increased inhibition of proliferation because pertuzumab also inhibits the heterodimerization of HER2 with HER3, and with increased ADCC activity due to the increased antibody density on the tumor cell membrane to favor activation of killing.

When trastuzumab controls disease progression primarily by blocking tumor cell proliferation, its use to deliver cytotoxic agents might represent an opportunity to overcome resistance. Trastuzumab-DM1, a conjugate consisting of trastuzumab linked to the microtubule poison maytansine, formulated to be nontoxic until it reaches its target site, has shown significant activity even in resistant tumor cells (24). A randomized phase II (NCT00679341) study in patients who never received chemotherapy for metastatic HER2-positive disease is ongoing to compare the efficacy of trastuzumab-DM1 vs trastuzumab plus docetaxel.

Because the testing of these new agents has been relegated to heavily pretreated patients, who may have already evolved to a state of high resistance to any type of therapy, the study of these agents is increasingly moving to earlier stages of the disease in the adjuvant and neoadjuvant setting. Examples include the GeparQuinto trial, which is comparing the efficacy of lapatinib with respect to trastuzumab in combination with chemotherapy patients with early breast cancer, and the NeoALTTO study (NeoAdjuvant Lapatinib and/or Trastuzumab Treatment Optimization), which is analyzing the clinical efficacy, based on complete disease disappearance, of lapatinib, trastuzumab, or both agents in combination followed by chemotherapy. Pertuzumab alone or in combination with trastuzumab with and without docetaxel is also being studied in women with HER2-positive early or metastatic breast cancer enrolled in the NeoSphere trial. Results of these trials with respect to safety and complete pathological response, presented at the 2010 San Antonio Breast Cancer Symposium, indicated the superior antitumor activity of combination HER2-targeted therapies (25–27).

Conclusions

In light of the different mechanisms of action of trastuzumab in different clinical settings, the response to this reagent should be assessed according to its ability to induce tumor cytotoxicity or cytostatic activity. Indeed, while RECIST criteria to evaluate effectiveness of targeted therapy are appropriate when trastuzumab kills neoplastic cells (ADCC and/or DNA repair inhibition), only overall and disease-free survival will accurately estimate trastuzumab efficacy when it acts primarily through inhibition of HER2-mediated proliferation signaling (Table 1). In the latter case, new imaging technologies that estimate the metabolic activity of the tumor and, in turn, reveal the extent of trastuzumab cytostatic action should be introduced into clinical practice.

Although much work remains in refining and optimizing anti-HER2 reagents and their application in patients, the known clinical benefits of targeting the HER2 molecule promise to justify such efforts. Indeed, the synergistic antitumor activity of trastuzumab in combination with chemotherapy in the neoadjuvant setting indicates the relevance of this association and the need for further investigation with respect to particular chemotherapeutic drugs and their optimal clinical use. Ongoing neoadjuvant trials promise to clarify whether a combination of targets agents is superior to any single agent alone.

Table 1

Due to the inappropriate use of response evaluation criteria. Indeed, only disease progression is indicative of trastuzumab ineffectiveness in blocking tumor growth (Table 1).
References


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