

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford A. Hudis, MD

Managing Trastuzumab-resistant Breast Cancer

Ian Krop, MD, PhD
 Assistant Professor of Medicine
 Harvard Medical School
 Associate Physician
 Dana-Farber Cancer Institute
 Boston, Massachusetts

H&O Can you describe the mechanism of trastuzumab resistance?

IK There have been a number of postulated mechanisms to explain trastuzumab (Herceptin, Genentech) resistance, most of which have been developed from work done with preclinical models. Unfortunately, very few of these theories have been validated in human clinical specimens because tissue samples from patients who have developed resistance are scarce. This is because acquiring samples from patients after they have developed resistance would mean multiple biopsies in the metastatic setting, which is not typically done. Therefore, although many mechanisms have been proposed, what actually occurs in the clinical situation is still largely unclear.

One potential resistance mechanism is that HER2 on the surface of the cell is downregulated, so that HER2-directed therapies such as trastuzumab no longer have a target. A study by Dr. Elizabeth Mittendorf from M.D. Anderson Cancer Center examined the residual tumors in patients treated with preoperative chemotherapy and trastuzumab and found that 30% had downregulation of HER2 expression (ie, tumors that started HER2-positive and were found to be HER2-negative after treatment), suggesting that at least in some patients, cancers can become resistant by losing HER2 expression.

Other mechanisms run the gamut. It has been proposed that other receptor tyrosine kinases can take the place of HER2, such as Met and the IGF-1 receptor, both

of which have laboratory-based data to suggest that they could be a factor in resistance. However, these hypotheses have not been confirmed in clinical specimens. Presently, the mechanism that is best supported by data is the constitutive activation of signaling pathways downstream of HER2, so that tumors no longer need the HER2 signaling, and therefore inhibiting HER2 is ineffective. The best example of this is activation of the PI3-kinase pathway: there have been several papers demonstrating that activation of the PI3-kinase pathway either through mutations in PI3-kinase itself or through loss of the tumor suppressor PTEN can lead to resistance to trastuzumab-based therapy. Supporting this hypothesis, several small retrospective studies have shown an association between activation of the PI3-kinase pathway and loss of sensitivity to trastuzumab-based therapy.

H&O What are the traits of patients who are resistant to trastuzumab?

IK It is hard to specify the traits of patients who are resistant because it is difficult to define resistance. Trastuzumab is not typically given by itself, but in combination with other treatments, most often chemotherapy. When someone develops resistance to chemotherapy plus trastuzumab, it is difficult to say whether that is resistance to trastuzumab or to the chemotherapy. Accumulating evidence suggests that it is actually the chemotherapy that patients are becoming resistant to, and that their tumors still retain some sensitivity to trastuzumab. Several studies have demonstrated that if someone whose cancer progresses on trastuzumab-based treatment switches

chemotherapy but continues trastuzumab therapy, they do better than on chemotherapy alone. This indicates that trastuzumab continues to add benefit even after progression on a prior trastuzumab therapy. One example is a study by O'Shaughnessy and colleagues, in which the trastuzumab plus lapatinib (Tykerb, GlaxoSmithKline) arm did better than lapatinib alone, despite the fact that patients had multiple lines of trastuzumab in the past. Also, a German study demonstrated that the continuation of trastuzumab with capecitabine is more effective than capecitabine alone.

Resistance to trastuzumab is a vague characteristic that is hard to pin down because continuing trastuzumab apparently offers benefits even after multiple lines. This is good news because it means that patients still derive benefit from a relatively nontoxic drug. It also indicates that HER2 remains an important target in these cancers even after progression, which provides hope that novel HER2-targeted therapies may provide additional benefit in this setting.

H&O What is the best approach to managing patients who are trastuzumab resistant?

IK There are a number of promising drugs in the pipeline, and the only way to know which are beneficial is by putting patients on clinical trials. Therefore, patients, particularly for this subgroup of cancers, are strongly encouraged to participate in clinical trials. Outside of a trial, the HER1/HER2 kinase inhibitor lapatinib, when combined with capecitabine is an effective option.

H&O Has there been any clinical evidence that combination therapy is more effective than single-agent therapy in treating refractory metastatic breast cancer?

IK There have been some isolated studies that seem to demonstrate that combination chemotherapy in certain instances provides increased responses and, occasionally, prolonged survival compared to single-agent chemotherapy. However, there are flaws in some of these studies and therefore, it can be argued that sequential single-agent chemotherapy is a less toxic and comparably effective treatment. My personal preference is to use sequential monotherapy rather than combinations.

When talking about targeted therapy, in most cases combining targeted therapy with chemotherapy is more effective than targeted therapy alone. While it would be ideal, in order to minimize toxicity, if targeted therapies alone were highly effective in patients, it is clear that combining targeted therapies such as lapatinib and trastuzumab with chemotherapy has significant synergy

and is probably the right way to manage most patients. Most data support this combination.

That said, there are patients who have good responses to chemotherapy plus a targeted agent like trastuzumab, who then can be transitioned to just the targeted agent alone and do quite well for a prolonged period of time.

H&O What new agents are currently being investigated?

IK One of the more promising agents is trastuzumab-DM1, which is trastuzumab chemically linked to a small molecule antimicrotubule agent. This is an agent that, in phase I/II trials, has demonstrated encouraging levels of activity in patients who had progressed on trastuzumab based therapy. It is also well tolerated and is now moving into later stage development.

Other drugs that Dana Farber Cancer Institute is investigating are the so-called "next generation" dual kinase inhibitors. These drugs, like lapatinib, inhibit EGFR and HER2; currently, 2 of them have been evaluated at our center. One is HKI272, which was evaluated in a phase II study led by Dr. Harold Burstein, and the other one is BIBW2992, which is also currently in phase II testing.

These drugs differ from lapatinib in that they are irreversible kinase inhibitors. Whereas lapatinib is a competitive inhibitor and can come off and on the kinase, these drugs become covalently linked once they bind the ATP pocket of HER2 or EGFR. There are some laboratory data suggesting that this might be a beneficial characteristic, but it will require head-to-head comparisons to determine if this difference in mechanism is clinically relevant.

Several other HER2-targeted agents are currently in development at other institutions; pertuzumab (Genentech) is another HER2-directed monoclonal, but it differs from trastuzumab in that it is able to block dimerization between HER2 and other HER family members. This drug shows activity when combined with trastuzumab and is currently in phase III studies in first-line metastatic HER2-positive disease. A phase II study of ertumaxomab (Fresenius Biotech GmbH), a HER2/neu and CD3-directed monoclonal, in patients with HER2-positive metastatic breast cancer who progressed on trastuzumab is also under way. Phase I results with this agent found a strong T helper cell type 1-associated immune response and antitumor efficacy. Another agent, tanespimycin, (Kosan Biosciences) inhibits the chaperone protein HSP90 and leads to degradation of HER2. Dr. Shanu Modi and colleagues at Memorial Sloan-Kettering Cancer Center have demonstrated significant efficacy with the combination of tanespimycin and trastuzumab in patients who have progressed on prior trastuzumab-based therapy.

H&O What challenges do you see in treating this disease in the refractory setting, and how can clinicians overcome these barriers?

IK One sobering point is that while there are several approved drugs for HER2-positive cancers, and there likely will be more in the fairly near future, none of these are curative in the metastatic setting. Patients' cancers will still develop resistance over time and we will still have to identify new therapies. The other point to remember is that HER2-positive disease, when there is no effective therapy, can be a very rapidly advancing and quite aggressive cancer. It still has a predilection for going into the central nervous system (CNS), where some HER2 targeted drugs cannot reach. CNS metastasis can be clinically devastating and a significant concern because options, once it occurs, are limited. There is certainly a great interest in attacking CNS metastases in a targeted way, and researchers have looked at some of the small molecules that cross the blood-brain barrier.

Another challenge is optimally managing the use of different HER2-targeted agents. Currently, it is not yet clear which HER2-positive cancer is best treated by trastuzumab and/or lapatinib. In the next 3 or 4 years, there will likely be additional drugs, and distinguishing which drug is best for which patient will get even more complicated. In order to avoid empirical treatment, participating in trials, obtaining biopsies on trials, and conducting robust correlative studies with those trials will be essential to determine which drugs are best suited for an individual patient.

Suggested Readings

O'Shaughnessy J, Blackwell KL, Burstein H, et al. A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2008;26:1015.

Burstein H, Awada A, Badwe R, et al. HKI-272, an irreversible pan erbB receptor tyrosine kinase inhibitor: Preliminary phase 2 results in patients with advanced breast cancer (abstract 6061). Presented at the 30th Annual San Antonio Breast Cancer Symposium; Dec 13–16, 2007; San Antonio, TX.