ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Breast Cancer in Focus

Treatment of Trastuzumab-Refractory, HER2-Positive Metastatic Breast Cancer

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H&O How common is resistance to trastuzumab (Herceptin, Genentech) in human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer?

SH Some patients with HER2-positive breast cancer in the metastatic setting experience de novo tumor resistance to first-line therapy, and the rest typically experience acquired resistance after an initial benefit from therapy. In 2002, Chuck Vogel published a study of single-agent trastuzumab as first-line treatment for HER2-positive metastatic disease, and found that about one-quarter of the patients had a tumor response to single-agent trastuzumab and close to 40% of patients had a clinical benefit. In other words, more than 60% of patients did not have tumor shrinkage or prolonged stable disease with trastuzumab.

A number of studies have found that when a combination of trastuzumab and chemotherapy is used as first-line treatment, the percentage of patients whose disease responds is between 40% and 60%, depending on the regimen. Even with combination treatment, however, most patients whose disease responds to first-line therapy will ultimately experience disease progression. These patients then go on to receive subsequent lines of therapy.

In my own practice, I would estimate that between 5% and 10% of patients achieve a prolonged or durable remission with first-line treatment of HER2-positive metastatic disease. I have a few patients whose disease has not progressed in the 5 years after first-line therapy, and 1 patient whose disease remained controlled on first-line trastuzumab-based therapy for 18 years. Only recently did her disease progress. This is an unusual situation in general, but it is seen more frequently in HER2-positive breast cancer than in other subtypes of breast cancer, in my experience.

H&O What are the causes of trastuzumab resistance?

SH There are many hypothesized mechanisms of resistance, some of which are better validated clinically than others. Loss of expression of the extracellular portion of the HER2 protein may be one mechanism of resistance. When this occurs, trastuzumab is unable to bind to HER2 on the cell and instead may be bound in the serum by free HER2 extracellular domain.

Activation of signaling pathways—such as the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway—via activating mutations of *PI3K* or *Akt* or downregulation of phosphatase and tensin homolog may also allow tumor cells to proliferate, even when HER2 is blocked by trastuzumab. Ongoing studies are evaluating the combination of drugs that block HER2 with drugs that inhibit 1 or more components of the PI3K/Akt/mTOR pathway.

One of these studies is BOLERO-3 (Daily Everolimus in Combination With Trastuzumab and Vinorelbine

in HER2/Neu Positive Women With Locally Advanced or Metastatic Breast Cancer). Ruth O'Regan reported data from this phase 3 study at the 2013 meeting of the American Society of Clinical Oncology (ASCO). The data showed an improved progression-free survival in patients with heavily pretreated HER2-positive metastatic breast cancer who received the mTOR inhibitor everolimus (Afinitor, Novartis) plus chemotherapy and trastuzumab compared with chemotherapy and trastuzumab alone.

Other signaling pathways that have been implicated in acquired resistance to trastuzumab are the Ras/Raf/mitogen-activated protein kinase pathways; upregulation of other receptors and pathways including insulin-like growth factor receptor, endothelial growth factor receptor (EGFR), and HER3; and increased expression of ligands to HER3, such as neuregulin.

Many potential mechanisms of resistance exist, making it challenging to know in an individual patient which pathway is most responsible for the resistance.

H&O What has been the effect of current regimens for metastatic HER2-positive breast cancer on trastuzumab resistance?

SH I think our ability to delay treatment resistance is improving with current regimens. Until recently, the standard regimen for first-line HER2-positive metastatic breast cancer included trastuzumab plus chemotherapy, but that approach has changed based on the results of the CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) trial and the subsequent US Food and Drug Administration (FDA) approval of pertuzumab (Perjeta, Genentech) in 2012. This study showed that patients who received trastuzumab/pertuzumab/docetaxel had a significantly longer progression-free survival than those who received trastuzumab/docetaxel, and they also had better overall survival in the updated analysis by Sandra Swain in *Lancet Oncology*. So it does appear that the addition of pertuzumab to trastuzumab helps delay—and possibly, in some, circumvent—resistance. Like trastuzumab, pertuzumab binds to HER2, but it prevents the HER2/HER3 heterodimerization.

After disease progression, patients have been typically offered lapatinib-based therapy or a different chemotherapy paired with trastuzumab. Now, based on the results of EMILIA (An Open-Label Study of Trastuzumab Emtansine [T-DM1] vs Capecitabine + Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer), patients whose disease progresses on trastuzumab are able to receive trastuzumab emtansine (TDM-1; Kadcyla, Genentech), which was approved in 2013. This gives patients a treatment option that is less toxic and appears to be more effective than traditionally delivered chemotherapy.

H&O What treatment options are available after second-line therapy has failed?

SH A number of options are available after patients have received TDM-1, but we have very little data to guide us on the best order of therapy or the best combinations of agents. Most of the studies beyond the first-line setting have been single-arm phase 2 studies, though a few phase 3 studies also have been done. I think that the general principle we need to follow in third-line therapy and beyond is continuing to target HER2 in a disease that is HER2-driven. That could mean using trastuzumab, lapatinib, or an experimental HER2-targeted agent as part of a clinical trial. The choice depends on the patient's goals, comorbidities, performance status, and desired treatment schedule. In general, I will continue to treat with subsequent lines of therapy as long as a patient desires further therapy and as long as her performance status is reasonably good. I find that trastuzumab with vinorelbine is quite well tolerated, although it does produce neuropathy and is a weekly regimen. Some patients do not want to be in the infusion room every week.

I have also used lapatinib in combination with trastuzumab. I think that Kimberly Blackwell's data on this combination are compelling. The use of these 2 agents together appears to be synergistic, even in the face of heavily pretreated disease that has progressed on trastuzumab in the past. Lapatinib and capecitabine is another reasonable option that I tend to use in patients who have disease of the central nervous system, because it appears to penetrate the central nervous system better than other regimens. In addition, a variety of options are available that use a HER2-targeted therapy in combination with medications such as cyclophosphamide, methotrexate, and fluorouracil (CMF), gemcitabine, and taxanes.

H&O Could you describe your recent study looking at TDM-1?

SH This phase 2 study was the first randomized clinical trial to look at TDM-1 in the first-line setting. A total of 137 patients were randomly assigned to receive either TDM-1 or docetaxel/trastuzumab. Although both groups had a similar response rate and clinical-benefit rate, the progression-free survival was significantly longer in patients receiving TDM-1, by about 5 months. TDM-1 also had better tolerability than docetaxel/trastuzumab; there were fewer grade 3 and 4 adverse events in the TDM-1 arm.

Although these data are exciting, this was a phase 2 study and so the results are not yet applicable to clinical practice. We are anticipating the results of the MARIANNE (A Study of Trastuzumab Emtansine [T-DM1] Plus Pertuzumab/Pertuzumab Placebo Versus Trastuzumab

[Herceptin] Plus a Taxane in Patients With Metastatic Breast Cancer) study, which is a phase 3 trial designed to clarify whether TDM-1 should be used in the first-line setting as a single agent or in combination with pertuzumab.

H&O What other approaches are being investigated for use in trastuzumab-resistant disease?

SH As mentioned earlier, the BOLERO-3 trial looked at the mTOR inhibitor everolimus in combination with trastuzumab and vinorelbine. Eligible patients had rather heavily pretreated, trastuzumab-resistant disease. This study showed that the addition of everolimus to vinorelbine/trastuzumab improved progression-free survival by about 5 weeks. The overall survival data are not yet mature.

Everolimus was FDA-approved in 2012 for estrogen receptor (ER)-positive, HER2-negative disease, at a dose of 10 mg daily. It is important to note that, based on safety data from phase 1 and 2 studies, BOLERO-3 utilized a 5-mg daily dose of everolimus.

Subset analyses of the study were interesting, and have generated some intriguing hypotheses. For example, tumors that were ER-negative and HER2-positive appeared to benefit more from everolimus than those that were ER-positive and HER2-positive. It is possible that in ER-positive, HER2-positive disease, we should be using hormonal blockade in combination with everolimus and trastuzumab rather than with chemotherapy. This hypothesis has not yet been evaluated in trials, however.

Other approaches that are being examined include the use of newer antibody-drug conjugates directed at HER2 or other targets expressed on the tumor cell. Other agents that are making their way through clinical trials are heat shock protein 90 (HSP90) inhibitors and inhibitors that target the PI3K/Akt pathway. Vaccine trials are also underway for patients with HER2-positive disease. It is an exciting time to be involved in the treatment of HER2-positive disease, given the availability of so many targeted agents both within and outside of clinical trials.

Suggested Readings

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