

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford A. Hudis, MD

Breast Cancer In Focus

Next-Generation Targeted Agents in HER2-Positive Metastatic Breast Cancer



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H&O What percentage of women with breast cancer have HER2-positive disease?

EP Data from the last several years suggest that approximately 15–20% of women with invasive breast cancer have human epidermal growth factor receptor 2 (HER2)-positive disease. Older studies had reported rates as high as 30%. HER2-positive disease tends to manifest differently from HER2-negative disease. HER2-positive patients are more likely to present with metastatic disease and develop brain metastases.

H&O How is HER2-positive disease identified?

EP There are several ways to test for HER2. The tumor specimen can be tested for the HER2 protein and the *HER2* gene with various testing kits. Immunohistochemistry is used to test for the HER2 protein, and fluorescence (or chromogenic) in situ hybridization (ISH) is used to evaluate the *HER2* gene. We have learned over the years that there can be some difficulty with the accuracy of these tests. In 2002, our group was one of the first to document a discordant rate as high as 20% between HER2 testing performed in a central laboratory as compared to a local laboratory. In newer adjuvant trials, we have continued to compare test results from local and central laboratories, as well as work with national and international organizations to optimize HER2 testing.

Another issue concerning HER2 testing is the continued confusion that exists regarding the cutoff level for

positivity. This controversy has been partially generated by the availability of 2 sets of criteria. The criteria approved by the US Food and Drug Administration (FDA) was used for all of the original adjuvant and metastatic HER2-positive trials. In 2007, guidelines from the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) defined new levels for positivity. Differences in these guidelines include the percentage of invasive tumor cells found on immunohistochemistry (10% for the FDA criteria vs 30% for the ASCO/CAP criteria). Although the ASCO/CAP guidelines were not intended to be utilized for treatment decisions, all pathologists are mandated to use them for reporting. The existence of these 2 sets of criteria has generated significant confusion, which may have led to undertreatment of some patients who were eligible to receive anti-HER2 therapy. Continued work is being done in this area, and the ASCO/CAP guidelines will be revised in 2012 to help alleviate the confusion. My colleagues and I recently published an article on this topic in the *Journal of the National Cancer Institute*. This issue is extremely important because if the tumors are not appropriately tested for HER2, then patients may miss the opportunity to benefit from effective therapies.

H&O Have any useful biomarkers been identified?

EP Researchers are interested in unraveling whether there are other molecular markers that may help better predict response to anti-HER2 therapy, beyond appro-

appropriate HER2 testing alone. Data should become available in the next few years. In the adjuvant setting, we have looked at multiple biomarkers, such as PTEN, protein expression, c-Myc, and the IGF-1 receptor. None have been predictive of outcome, based on data so far. We were very interested in data concerning HER3, but this marker was not predictive, either. There is potential that HER1 might be important, and we are looking at multigene profiles to identify any additional information. Moreover, we are also planning to examine a P95 assay, which has not been possible until now due to the lack of a validated assay.

H&O How are HER2-positive patients treated?

EP There are several options for these patients. Some patients with estrogen receptor (ER)-positive breast cancer are treated with antiestrogen therapy alone. However, data from 2 studies—TANDEM (Trastuzumab in Dual HER2 ER-Positive Metastatic Breast Cancer) and the lapatinib (Tykerb, GlaxoSmithKline) trial by Johnston and colleagues—showed that antiestrogen therapy alone does not achieve a good outcome in patients with ER-positive, HER2-positive disease. There may be a few patients with very indolent disease who could potentially benefit from antiestrogen therapy alone. But even among these patients, the majority would receive anti-HER2 therapy in combination with antiestrogen. Many of these patients present with visceral metastases.

We tend to use chemotherapy in combination with trastuzumab (Herceptin, Genentech) as first-line therapy. However, new data from the CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) trial have demonstrated that a better approach may be the combination of chemotherapy with trastuzumab and the other monoclonal antibody, pertuzumab (Omnitarg, Genentech). This triple-drug regimen has recently received FDA approval in the first-line HER2-positive setting.

Another important area for clinical practice and research is which chemotherapy should be used in combination with the anti-HER2 treatment. Traditionally, we have used taxanes. Other possible regimens include weekly paclitaxel in combination with weekly carboplatin as the backbone chemotherapy regimens. Vinorelbine (Navelbine, GlaxoSmithKline) might also be used. The goal is to find the best combination treatment with the least toxicity, while optimizing tumor shrinkage, progression-free survival (PFS), and overall survival. An ongoing study, VELVET (A Combination of Pertuzumab, Trastuzumab, and Vinorelbine for First-Line Treatment of Patients With HER2-Positive Metastatic Breast Cancer: An Open-Label, Two-Cohort, Phase II Study), is evaluating vinorelbine with trastuzumab and pertuzumab in the first-line setting.

H&O Are there any new or ongoing clinical trials in HER2-positive disease?

EP Capecitabine (Xeloda, Genentech) plus lapatinib is the only regimen approved by the FDA and other regulatory agencies around the world for these patients, but this is expected to change based on a recently completed and reported clinical trial. There has been much interest in trastuzumab emtansine (Genentech), also known as T-DM1, in the second-line and third-line settings. The EMILIA (An Open-Label Study of Trastuzumab Emtansine [T-DM1] vs Capecitabine+Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer) trial, presented at the 2012 ASCO meeting, compared T-DM1 versus the combination of capecitabine with lapatinib in HER2-positive locally advanced or metastatic breast cancer. T-DM1 significantly prolonged PFS (9.6 months vs 6.4 months [hazard ratio, 0.650; 95% confidence interval, 0.55–0.77; $P < .0001$]) and improved overall survival at 1 year (84.7% vs 77.0%) and 2 years (65.4% vs 47.5%).

There is also significant interest in evaluating T-DM1 in the first-line setting. We recently conducted a randomized, phase II trial evaluating T-DM1 in the first-line setting. Data were presented at the 2010 and 2011 European Society for Medical Oncology (ESMO) meetings. We enrolled 137 patients, who received either a taxane/trastuzumab combination or T-DM1. PFS was much better in the T-DM1 group.

I am involved in the conduct of a robust, phase III global trial called MARIANNE (A Study of Trastuzumab Emtansine [T-DM1] Plus Pertuzumab/Pertuzumab Placebo Versus Trastuzumab [Herceptin] Plus a Taxane in Patients With Metastatic Breast Cancer). We recently completed accrual of 1,094 patients eligible to receive first-line chemotherapy with anti-HER2 therapy for metastatic breast cancer. This trial compares 3 arms: trastuzumab, in combination with a taxane (either docetaxel once every 3 weeks or paclitaxel once every week); T-DM1 alone; and T-DM1 in combination with pertuzumab.

H&O What other novel agents are under investigation?

EP Another agent under investigation is neratinib, which appears to be similar to lapatinib in terms of mechanism of action, but appears to have an increased rate of gastrointestinal toxicity. There is also interest in looking at other agents that do not target HER2 per se, but may enhance activity. Everolimus (Afinitor, Novartis), a mammalian target of rapamycin (mTOR) inhibitor, is being studied in combination with trastuzumab in the first-line setting in the BOLERO-1 (Breast Cancer

Trials of Oral Everolimus) trial and in the refractory setting in the BOLERO-3 trial. BOLERO-1 is evaluating a taxane plus trastuzumab with or without everolimus in the first-line setting, and BOLERO-3 is testing vinorelbine plus trastuzumab with or without everolimus in the refractory HER2-positive setting.

H&O What are some areas of future research?

EP One of the many important areas of research is the need to identify the percentage of patients who present with metastatic disease who also have brain metastases that are silent. We are finding more and more of these patients. In the short-term future, there may be a change in the recommendations for staging of patients with metastatic HER2-positive breast cancer; these patients may need to undergo full positron-emission tomography (PET) scanning to identify any potential silent brain metastases. A related area of research is how to best manage brain metastases in these patients. The biopharmaceutical company Geron is exploring the development of a targeted method to deliver paclitaxel to patients who have tumors that are either HER2-positive or HER2-negative. The novel antibody Geron 1005 directs a payload to abnormal vasculature.

Management of patients with HER2-positive metastatic breast cancer should serve as an example of what can be accomplished with good science and good clinical trials to optimize the selection of patients who will benefit from novel therapies.

Suggested Readings

Blackwell KL, Miles D, Gianni L, et al. Primary results from EMILIA, a phase III study of trastuzumab emtansine (T-DM1) versus capecitabine (X) and lapatinib (L) in HER2-positive locally advanced or metastatic breast cancer (MBC) previ-

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Perez EA, Dirix L, Kocsis J, et al. Efficacy and safety of trastuzumab-DM1 versus trastuzumab plus docetaxel in HER2-positive metastatic breast cancer patients with no prior chemotherapy for metastatic disease: preliminary results of a randomized, multicenter, open-label phase 2 study (TDM4450G). *Ann Oncol* (ESMO Meeting Abstracts). 2010;21(suppl 8): Abstract LBA3.

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Tan WW, Allred JB, Salim M, et al. Phase II interventional study (N0337) of capecitabine in combination with vinorelbine and trastuzumab for first- or second-line treatment of HER2-positive metastatic breast cancer: a north central cancer treatment group trial. *Clin Breast Cancer*. 2012;12:81-86.

Verma S, Dieras V, Gianni L, et al. EMILIA: a phase III, randomized, multicenter study of trastuzumab-DM1 (T-DM1) compared with lapatinib (L) plus capecitabine (X) in patients with HER2-positive locally advanced or metastatic breast cancer (MBC) and previously treated with a trastuzumab-based regimen. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2011;29(suppl): Abstract TPS116.