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Breast Cancer In Focus

Importance of Accurate HER2 Testing in Patients With Metastatic Breast Cancer

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H&O What is the role of HER2 in breast cancer treatment?

AMG Human epidermal growth factor receptor 2 (HER2)/neu is an oncogene that codes for the HER2 protein. The gene is amplified and the protein is overexpressed in approximately 25% of breast cancers. In general, the breast cancers that overexpress the protein, or have gene amplification, have worse prognosis. Tumors that have HER2 overexpression are more aggressive and highly proliferative. Patients with HER2-positive tumors also have worse survival outcomes. Approximately 10 years ago, trastuzumab—a monoclonal antibody targeting HER2—was developed. This targeted therapy changed the natural history of HER2-positive breast cancer. At present, patients who have HER2-positive breast cancer have a much better prognosis with trastuzumab than they would have had 10 years ago.

HER2 assessment is essential for several reasons: it is a prognostic factor that correlates with aggressive tumors that result in higher risk of recurrence and mortality, and it is a predictive factor for response to anti-HER2/neu therapies. It is evident that the use of anti-HER2 therapies in patients with HER2 amplified tumors results in a reduction in the risk of recurrence by approximately 50%. Thus, HER2 assessment has a significant role in breast cancer treatment.

H&O What is the significance of accurate HER2 testing in patients with metastatic breast cancer?

AMG Accurate testing of HER2 status has become of great importance for patients with breast cancer since the availability of trastuzumab (Herceptin, Genentech). There are several HER2 assays approved by the US Food and Drug administration: immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and bright field in situ hybridization. Patients who have HER2-positive metastatic breast cancer have tumors that are very sensitive to anti-HER2 therapies. If we do not have accuracy in our testing, we fail to identify tumors that are HER2-positive, and therefore are not able to provide the best treatment for patients with metastatic disease. Furthermore, inaccuracy in testing may produce a false negative result (ie, a tumor we believe to be HER2-positive is actually HER2-negative), which means we are treating patients with the wrong therapy. Thus, accurate HER2 testing is critical.

In patients who have HER2-positive tumors who have been treated and have then relapsed, approximately 20% of the tumors become change receptor status. We do not know the significance of these changes, but we do know from some of the published data that when HER2 status changes from positive to negative, the prognosis becomes worse, probably because the tumors are no longer sensitive to anti-HER2 therapies. If this occurs, then we have to investigate other targeted therapy options for this group of patients.

H&O What are some reasons why there may be discordance in HER2 testing?

AMG There may be several reasons for discordance in HER2 testing, including the accuracy of the test and

quality control issues related to the laboratories that perform the test. Previous studies have found discrepancies in the assay testing done at central laboratories compared to those done at local hospital laboratories. Central pathology laboratories are usually high-volume laboratories that perform many HER2 assays, whereas local hospital laboratories may not have the same experience with HER2 testing. Therefore, the tests performed at central laboratories are more standardized, and there is a higher level of quality control.

Another reason for the discordance is tumor heterogeneity. When looking at a tumor, it is sometimes possible to see areas that are HER2-positive and areas that are HER2-negative. When a core biopsy is done, the needle might collect cells from an area that is HER2-negative, and then the test is HER2-negative, but if the needle is placed in the HER2-positive area, then the test is HER2-positive.

One of the other issues is that we do not know if HER2 status changes when patients are treated with anti-HER2 therapy. We have performed several studies investigating this question. One study, which has been recently published in the *Annals of Oncology*, showed that the use of trastuzumab did not correlate with changes in the tumor, so we do not really know the specific causes for these changes. For this reason, it is important to retest tumors because we cannot rely on the primary tumor histology at the time a patient develops metastases.

H&O How do we establish a standardized approach to HER2 testing?

AMG It is necessary for pathologists to understand HER2 assays such as IHC and FISH and to follow the American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP) guidelines, including participation in a proficiency testing program. The discordance in IHC testing has led to a combined effort from oncologists and pathologists in attempting to accurately test patients with breast cancer.

The use of autostainers that automatically dispense reagents and control washing, mixing, and heating of the specimen, and other instruments that provide consistency in testing have helped standardize HER2 screening; however, if the pathologist is not skilled in performing HER2 assays, then the use of this equipment is futile. We suggest that local laboratories send their specimens to a central pathology facility to confirm their findings when the clinical picture does not match the pathology results.

H&O What is the optimal testing algorithm for assessing HER2 status?

AMG The optimal testing algorithm is a strategy established by the ASCO/CAP that helps ensure the most favorable performance, interpretation, and reporting of HER2 assays. In this algorithm, test results are categorized as positive, negative, and equivocal. The first test that is recommended for a breast cancer specimen is IHC, which tests protein expression. If the IHC score is 3+, which is high intensity in greater than 30% of cells, it is considered a HER2-positive tumor. If the IHC score is 2+, the test is equivocal and requires confirmatory testing with FISH. If the IHC score is 0–1+, it is considered HER2-negative. The corresponding FISH test measures gene amplification in a ratio of the number of copies of the gene to the number of chromosome 17. A ratio of greater than 2.2 is considered HER2-positive, a ratio between 1.8 and 2.2 is equivocal, and a ratio of less than 1.8 is HER2-negative. If the FISH results are equivocal, confirmation by counting additional cells or repeating FISH is recommended.

It is important to teach people who work in the community as well as in the academic centers that if there is ever any doubt regarding the clinical information, the tumor behavior, or the status of the patient, it is essential to work with the pathologist in reviewing the case to establish accurate HER2 status.

H&O What do we hope to achieve with standardized and accurate HER2 testing?

AMG Accurate and standardized HER2 testing is paramount. A positive HER2 test is a prerequisite for patients who are going to respond to anti-HER2 therapy in the metastatic and adjuvant settings. There are many clinical trials evaluating anti-HER2 therapies, including trastuzumab-DM1, pertuzumab (Genentech), and neratinib (Pfizer) that can be given in addition to trastuzumab. Accuracy in HER2 testing allows for easier decision making in regard to the type of treatment to administer in this subset of patients.

Suggested Readings

Wolff AC, Hammond MEH, Schwartz JN, et al. College of American Pathologists. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. http://www.cap.org/apps/cap.portal?_nfpb=true&_pageLabel=reference. Updated October 16, 2009.

Grimm EE, Schmidt RA, Swanson PE, Dintzis SM, Allison KH. Achieving 95% cross-methodological concordance in HER2 testing: causes and implications of discordant cases. *Am J Clin Pathol*. 2010;134:284-292.