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Current Developments in the Management of Solid Tumor Malignancies

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Breast Cancer In Focus

The Importance of Accuracy in HER2 Testing

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H&O Why is assessment of HER2 status in breast cancer patients important?

AG Assessment of human epidermal growth factor receptor 2 (HER2) status can identify patients who would benefit from anti-HER2 therapy, either in the early breast cancer setting or in the metastatic breast cancer setting. Anti-HER2 therapy has been shown to improve disease-free survival and overall survival in patients with early breast cancer, and to increase progression-free survival and overall survival in patients with advanced breast cancer. HER2 is an important biomarker because it has consequences. If we fail to detect HER2, we fail to give patients the appropriate therapy, and they may die from incurable disease.

H&O How is HER2 status assessed?

AG There are 2 main ways to assess HER2 status that are approved and considered standard. Immunohistochemistry evaluates the expression of the protein, which is a receptor that sits on the surface of the cell. Results are reported as no staining versus 1+, 2+, or 3+ according to the number of cells that are stained for the protein and the intensity of the staining. HER2-positive disease is considered 3 when it is apparent at high intensity in at least 30% of the cells, according to guidelines from the American Society of Clinical Oncology (ASCO) and the College of American Pathology (CAP).

The other way of measuring HER2 is by gene amplification, which can be done with fluorescent in situ hybridization (FISH) or chromogenic in situ hybridization (CISH). These methods count the copies of the gene—not the protein—that are localized in the nucleus. The number is considered amplified when there are at least 2.2 copies.

ASCO and CAP have published guidelines to determine positive or negative status for HER2. The thresholds in these guidelines differ from those that were used in clinical trials evaluating anti-HER2 therapy. However, according to members of the expert panel that defined the guidelines, we should not withhold therapy in patients that meet the criteria for the adjuvant trials. Further, a study by Perez and colleagues examined patients in NCCTG9831 who had a gene amplification ratio from 2.0–2.2. These patients appeared to benefit from anti-HER2 therapy. Therefore, patients with a ratio of 2.0 or more gene amplifications should be treated with anti-HER2 therapy.

H&O How often is HER2 testing inaccurate, and what factors contribute to these inaccuracies?

AG The rate of inaccuracies often depends on where the testing is performed. Studies of central confirmatory testing in large clinical trials have compared central testing versus peripheral testing. Local centers are associated with a higher rate of inaccurate testing, both false posi-

tives and false negatives. All testing centers should follow updated recommendations from CAP and perform regular quality control testing.

A 2006 study by Perez and coworkers found a high degree of discordance between local and central testing for immunohistochemistry and FISH. When local and central evaluation used the same methodology, concordance was 88.1% for FISH and 81.6% for immunohistochemistry. When discordant cases were examined at a reference laboratory, there was 94.3% agreement for immunohistochemistry (0, 1+, 2+) and 95.2% agreement for FISH (not gene amplified).

Test results can be altered by several factors concerning both the testing methodology and the tumor. Factors influencing the test include tissue collection, tissue processing, staining, and interpretation of the immunohistochemistry results. Testing of the tumor can also be affected by tumor heterogeneity. Tumors can have areas of HER2-positive and HER2-negative cancer, and a sample drawn from a particular part of the tumor may not be indicative of the whole.

H&O What are the best ways to minimize inaccuracies?

AG There are 2 main ways to minimize inaccuracies. Pathologists should thoroughly know the testing process, be familiar with the latest ASCO/CAP guidelines, and maintain updated certification so that testing can be performed in optimal conditions. In the clinic, it is important to identify when retesting is necessary. An equivocal result, such as 2+ in immunohistochemistry or a gene amplification ratio of 1.8–2.0, warrants retesting with FISH and a repeat FISH or immunohistochemistry, respectively. Clinical parameters are also important. A clinician may choose to retest a tumor with an immunohistochemistry staining of 1+ in the setting of a high nuclear grade or in a young patient. Although this staining result is considered negative, approximately 10% of these patients in some series have been reported to have gene amplifications. A confirmatory test is inexpensive compared to the costs associated with inaccurate diagnosis.

H&O What characteristics suggest that a HER2-negative result may be incorrect?

AG As an example, a HER2-negative result may be incorrect in a young patient who has high-grade breast cancer that is rapidly growing and whose immunohistochemistry for HER2 is negative or equivocal. Such a patient would warrant a discussion with the pathologist. It is important to have open communication with the pathologist, and either repeat the test, send it to another laboratory, or use another technology.

H&O Can a patient's HER2 status change?

AG HER2 status can change for 2 reasons. A change in status may be attributable to a laboratory error. A patient with HER2-negative disease might have a recurrence that is biopsied and found to be HER2-positive. Immediately, the pathologist should be consulted and a retest arranged so that new test results can be compared with previous results to identify whether HER2 status really did change.

In addition, the tumor itself can change status. In a phenomenon known as tumor evolution, tumors change after being exposed to therapy. Anti-HER2 therapy can eradicate all of the cells that are HER2-positive, while sparing cells that are HER2-negative. In such a case, a relapsed tumor will be HER2-negative. A prospective clinical trial in Spain, the CONVERTHER (Evaluation of Degree of Conversion of HER2 Receptor Between Primary Breast Cancer and Metastasis) study from GEICAM (Grupo Español de Investigación del Cáncer de Mama) has recently completed accrual, and preliminary results were presented at the 2011 San Antonio Breast Cancer Symposium. A total of 236 patients were included in the study, and data are available for 183 paired cases that were centrally evaluated. More than half of patients (65%) were in first recurrence, and the mean age was 57.2 years. Benign lesions or secondary malignant neoplasms were identified in 6.6% of the normal tissue in biopsies. The changes in HER2, the estrogen receptor, and the progesterone receptor were 17%, 26%, and 35%, respectively, in local laboratory testing, and 4%, 12%, and 26%, respectively, in central laboratory testing. The concordance rates in HER2, the estrogen receptor, and the progesterone receptor between local and central testing were 83%, 92%, and 78%, respectively. Changes in the receptor status required treatment modification in 16% of patients. The authors concluded that there was a remarkable discordance in receptor status, especially in the hormonal receptors, between the primary tumor and metastases. These discordances were reduced after tests were performed in a high-quality central laboratory and are only partially attributable to technical discrepancies in receptor assessments.

Suggested Readings

Hammond ME, Hayes DF, Wolff AC. Clinical Notice for American Society of Clinical Oncology-College of American Pathologists guideline recommendations on ER/PgR and HER2 testing in breast cancer. *J Clin Oncol*. 2011;29:e458.

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and corresponding metastases. CONVERTHER/GEICAM 2009-03 study. Abstract presented at the San Antonio Breast Cancer Symposium; December 6-10, 2011; Abstract P2-12-17.

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