Saving Lives With Accurate HER2 Testing

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In December 1998, the US Food and Drug Administration simultaneously approved the antibody therapeutic trastuzumab (Herceptin, Genentech, South San Francisco, CA) for the treatment of HER2 overexpressing invasive breast cancer and the immunohistochemically based diagnostic test (HercepTest, DAKO, Glostrup, Denmark) designed to select patients for this novel targeted treatment. Today, more than 11 years later, anti-HER2 targeted therapy for breast cancer has become a cornerstone for treatment of HER2+ disease, with unprecedented success achieved with the use of trastuzumab and the more recently approved tyrosine kinase small molecule inhibitor lapatinib (Tykerb, Glaxo Smith Kline, Philadelphia, PA) in adjuvant and neoadjuvant metastatic disease settings. When given early in the course of disease, these drugs have achieved a major impact on patient survival. Thus, the importance of accurately identifying HER2+ breast cancer has never been greater.

In their article that appears in this issue of the Journal, Grimm et al describe several novel approaches used in their evaluation of 697 cases of breast cancer at the University of Washington for concordance between the 2 prevalent methods of HER2 testing, immunohistochemical analysis and fluorescence in situ hybridization (FISH). The authors studied cases in which immunohistochemical analysis and FISH had been performed according to the prevailing American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines published in 2007.

After the authors noted that, in their laboratory, the concordance between unequivocal immunohistochemical and FISH results was 96%, they attempted to review each discordant case in detail to find possible explanations for the discordant cases. Grimm et al concluded that immunohistochemical interpretation was the major cause of the immunohistochemically positive, FISH-negative discordance, with overinterpretation of weak membranous staining intensity, crush and sample edge artifacts, and inclusion of granular cytoplasmic staining as the causes of likely original false-positive immunohistochemical results. For the immunohistochemically negative, FISH-positive discordant cases, the authors noted that 2 of 6 patients were already receiving trastuzumab-based treatment and that 4 of 6 patients may have had false-positive HER2 FISH ratios driven by loss of chromosome 17 signals. Thus, by the use of meticulous technique, which included an evaluation of immunohistochemical staining with and without heat-induced epitope recovery (antigen retrieval), these authors have been able to confirm for themselves, their colleagues in oncology, and their patients that the HER2 testing performed in their institution exceeds the published ASCO/CAP standards and is performed under a continuing program of quality assessment.

The study by Grimm et al raises many issues of keen interest for pathologists who provide HER2 testing and for pathologists who refer their HER2 testing to other laboratories. In early 2010, it is estimated that 80% of the HER2 testing in the United States begins with immunohistochemical analysis (2+ cases referred for FISH testing) and 20% of testing is FISH only. The more recently approved chromogenic in situ hybridization test is not widely performed to date, although this is predicted to change after new nonfluorescent in situ hybridization tests are approved. Among the important HER2 testing issues, none is more important than the question: Which discordance has the most significant impact for patients?
False-Positive HER2 Result

Based on the data presented by Grimm et al., a false-positive HER2 result is most likely to be an immunohistochemically false-positive result due to inappropriate staining interpretation. If not “corrected” by a simultaneous FISH assay, patients with these results would likely be treated with a trastuzumab- or lapatinib-based regimen in the adjuvant or neoadjuvant setting with a significantly reduced chance of benefit. This would add cost and the risk of adverse events, such as the cardiac toxicity associated with this form of treatment. However, recent approaches to reduce cardiac toxicity of anti-HER2 targeted therapy have been successful in significantly reducing level 3 and level 4 adverse events, and studies of immunohistochemically positive, FISH-negative cases in which patients were treated with trastuzumab have described clinical benefit from this therapy in some cases. Thus, it is argued here that false-positive HER2 results do not have as serious an impact on patient outcome as do false-negative results.

False-Negative HER2 Result

Based on central review of clinical trial data in the adjuvant setting, mRNA results from the Oncotype Dx clinical assay (Genomic Health, Redwood City, CA), and transcriptional profiling laboratories, it is estimated that the results of 3% to 4% of primary HER2 testing are falsely negative. Given the high incidence of breast cancer in the United States, if the results of 3% to 4% of primary immunohistochemical and FISH HER2 testing are falsely negative, the care of from 3,000 to 5,000 US women each year could conceivably be negatively impacted. Given the approximate 50% reduction of relapse events when anti-HER2 targeted therapy is included in the adjuvant setting, one can now make the statement that each year, thousands of American women may be experiencing relapses from failed adjuvant regimens that would not have occurred if the cancers had been correctly identified as HER2+ and originally treated with trastuzumab- and/or lapatinib-based regimens. There can be little doubt that improving the accuracy of HER2 testing and reducing the incidence of false-negative results can literally save lives.

The HER2+ Rate: The First Screen for Accuracy

Although the authors do not report it separately, when FISH was used as a “gold standard” on the 697 cases that had FISH and immunohistochemical tests performed, their laboratory found 134 cases (19.2%) with HER2 amplification or HER2 copy number more than 6. A number of experts noted that, for programs with HER2+ rates below 10%, serious investigation of the testing procedures from the preanalytic steps covered in the ASCO/CAP guidelines to protection against false-negative immunohistochemical results associated with the absence of the 3+ positive control tissue located on the same slide as the patient’s tumor be undertaken. With the proven efficacy of anti-HER2 targeted therapy, especially when given at the time of diagnosis before systemic disease has developed, getting the HER2 test result right is a matter of life and death.

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References