Re: How Do You Tell Whether a Breast Cancer is HER2 Positive? Ongoing Studies Keep Debate in High Gear

Charlie Schmidt described several important issues related to current HER2 testing and interpretation in a recent issue of the Journal (1). He points out that there is continuing disagreement about the best assay for HER2 status assessment in breast cancer specimens—fluorescence in situ hybridization (FISH) or immunohistochemistry. Schmidt also correctly pointed out that the FISH ratio calculation, which was introduced to control for aneuploidy of chromosome 17, is no longer fully supported by clinicians. However, Schmidt stated that aneusomy is a common finding but did not mention the recent observation that chromosome 17 polysomy is far less common in breast cancer than previously suggested (2–5), and may in fact be very rare. Several independent studies using comparative genomic hybridization, FISH, and multiplex ligation-dependent probe amplification have shown that true polysomy 17 is an exceedingly rare event in breast cancer and that an increase in CEP17 copy number is often unrelated to the copy number of 17q, let alone the whole chromosome 17. It has therefore been suggested that increased centromere 17 signals detected in invasive breast carcinomas may lead to discordant interpretation of gene amplification in many specimens, depending on which criterion (ratio vs absolute number) is used for interpretation (6,7). An improper classification of breast cancer as chromosome 17 polysomic, on the basis of...
dual-probe in situ hybridization assays may at least in part be responsible for the counterintuitive reported benefit of trastuzumab for patients with an allegedly HER2-negative tumor. Increased gene dosage (>6 HER2 gene copies or a HER2/CEP17 ratio > 2.2), regardless of the evaluation method, is however positively correlated with HER2 protein expression \( (P < .01, r_s = 0.56 \text{ and } 0.64, \text{ respectively}) \) (6). Future prospective clinical trials should assess chromosome 17 status using methods other than or in addition to CEP17 and HER2 gene copy number to help elucidate the mechanism by which CEP17 or other pericentromeric chromosome 17 genes could possibly influence trastuzumab and lapatinib sensitivity.

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References


Notes

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