Evaluation of Her-2/neu Status in Carcinomas With Amplified Chromosome 17 Centromere Locus

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Abstract

Accurate assessment of Her-2/neu (erb-b2) status in breast carcinoma is essential for therapy planning. Clinical assays are targeted at protein overexpression (immunohistochemical analysis) or gene amplification (fluorescence in situ hybridization [FISH]). Cases with aberrant FISH signal patterns are problematic and may lead to underreporting of Her-2/neu amplification.

We performed FISH with additional chromosome 17 probes, SMS (Smith-Magenis syndrome critical region) and RARA (retinoic acid receptor), on 7 cases with unusual Her-2/CEP17 (chromosome 17 centromere control probe) results to assess whether different measurements of chromosome 17 copy number might clarify the Her-2/neu amplicon status. Although the Her-2/CEP17 ratio scores were within normal range (<2.0), the Her-2/SMS or Her-2/RARA ratio revealed amplification of Her-2/neu in 5 of 7 cases. Immunohistochemical analysis demonstrated Her-2/neu protein overexpression in the same 5 cases only.

We describe novel application of SMS/RARA FISH probes for assessing cases with complex Her-2/CEP17 FISH patterns. Such additional data, correlated with immunohistochemical analysis, may help guide therapy in patients with breast carcinoma.

Research in tumor diagnosis and treatment has led to the discovery of numerous prognostic and predictive markers for breast carcinoma. Current patient management relies on a number of ancillary studies, including estrogen receptor (ER), progesterone receptor (PR), and Her-2/neu (erb-b2) protein overexpression and/or gene amplification status. It has been known for many years that the 20% to 30% of breast carcinomas overexpressing Her-2/neu have a poor prognosis compared with those with normal levels and may respond differently to cytotoxic chemotherapy.1-4 These tumors often are high grade, with a high proliferation rate and a propensity for lymph node involvement.3,4 Recently, these tumors have been found to have distinct molecular profiles.5-9 The Her-2/neu (erb-b2) oncogene encodes a 185-kd tyrosine kinase receptor of the epidermal growth factor receptor family, although a unique ligand has not been identified.3 In the majority of cases, Her-2/neu protein overexpression correlates well with amplification of the Her-2/neu locus on the chromosome 17 long arm.2,4

With the Food and Drug Administration (FDA) approval of trastuzumab (Herceptin) in 1998, targeted therapy has become available for Her-2/neu–overexpressing tumors. This humanized monoclonal antibody initially was used to treat patients with Her-2/neu+ metastatic disease, with a response rate of 20% to 35%.10-12 However, recent data from US and European studies have identified a significant benefit of first-line trastuzumab therapy, in conjunction with surgery and cytotoxic chemotherapy.13,14 Thus, the correct identification of Her-2/neu+ breast carcinomas is an important component of the pathologic evaluation of breast carcinoma specimens.

Her-2/neu studies originally were performed with biochemical assays requiring fresh frozen tissue samples3,4,
subsequently, immunohistochemical methods to detect Her-2/neu overexpression at the cell membrane, performed on archived, formalin-fixed, paraffin-embedded tissue samples, have been implemented in many pathology laboratories.\(^3,4\) Fluorescence in situ hybridization (FISH) assays to evaluate gene amplification also allow paraffin slide–based assessment of Her-2/neu and correlation with morphologic features. There are 2 FDA-approved immunohistochemical assays (HercepTest, DAKO, Carpinteria, CA, and PATHWAY, Ventana, Tucson, AZ) and 2 FDA-approved FISH assays (INFORM, Ventana, and PathVysion, Abbott-Vysis, Des Plaines, IL). Many laboratories use immunohistochemical analysis as a primary assay, with “flex” FISH testing of a specific subset of immunohistochemical results (eg, 2+, or 1+, 2+), and other laboratories use FISH primarily.\(^15,16\) Of note, novel methods, including those with immunohistochemical analysis and in situ hybridization developed on the same tissue section, are under investigation and validation.\(^17\)

As experience with assay methods has accumulated, cases with aberrant immunohistochemical or in situ hybridization patterns have been described. These include cases with heterogeneous tumor populations revealed by FISH and cases with chromosome 17 aneusomy. A number of small studies have addressed chromosome 17 polysomy\(^2,18-23\); however, rare cases with apparent amplification of the chromosome 17 control FISH probe at the 17 centromere (CEP17), present in the Abbott-Vysis reagent, also have been identified.\(^24\) In this situation, the calculated Her-2/CEP17 ratio is low, and this ratio may not reflect real Her-2/neu status, denying patients targeted therapy. We tested FISH probes to the chromosome 17 loci SMS (Smith-Magenis syndrome) and RARA (retinoic acid receptor) as surrogate chromosome 17 controls in 7 cases with a high copy number of CEP17, in correlation with Her-2/neu immunohistochemical analysis.

**Materials and Methods**

The files of the Stanford University Medical Center Cytogenetics Laboratory (Stanford, CA) were searched for Her-2/neu FISH assay results with aberrant CEP17 control probe signals not accounted for by aneusomy 17, described as CEP17 amplification for the purposes of this study. We identified 6 cases with CEP17 greater than 125/25 cells and a Her-2/CEP17 ratio of 1.0 or less.

These cases were identified from 858 FISH assays as follows: between March 2002, when the test was first offered, and January 2004, 134 assays were performed (during this time FISH was performed as a confirmatory test for cases with a 2+ immunohistochemical score or by clinician special request); between February 2004 and December 2005, 724 assays were performed (during this time, FISH was used as the primary assay method). An additional case was incorporated from Oregon Health & Science University (OHSU, Portland; prevalence data not available), for a total of 7 study cases. Two of these cases were consultations sent for Her-2/neu testing, whereas the remainder, including the OHSU case, were encountered as routine surgical pathology specimens. Tumor type, size, and nodal status were extracted from pathology reports; slides were reviewed to confirm tumor differentiation, grade, and ER and PR status.

Cases 1 and 2 were high-grade infiltrating ductal carcinomas with syncytial (atypical medullary) and micropapillary features, respectively. Case 6 was a high-grade ovarian carcinoma with serous papillary features. The other breast cases were ductal carcinomas of no special type; case 7 was a needle core biopsy specimen, for which no further information is available. Follow-up data regarding outcome or response to trastuzumab therapy, unfortunately, is not available.

Her-2/neu FISH was performed on 4-µm paraffin sections using the FDA-approved PathVysion kit. Briefly, this assay uses a probe for the Her-2/neu locus (17q12, SpectrumOrange) and CEP17 as the chromosome 17 control probe (D17Z1, 17p11.1-q11.1, SpectrumGreen). Deparaffinization, hybridization, washing, and counterstaining were performed according to the manufacturer’s instructions. Fluorescence was visualized on a CytoVysion image capture system (Applied Imaging, San Jose, CA) with an Olympus BH51 (Olympus, Center Valley, PA) or a Nikon E800 (Nikon, Melville, NY) microscope with multiple filters, including DAPI (4,6-diamidino-2-phenylindole), spectrum orange, spectrum green, as well as dual-pass, and correlated directly with hematoxylin- or H&E-stained tissue sections to ensure scoring of invasive carcinoma. Her-2/neu and CEP17 signals were enumerated in 25 cells, and a total Her-2/CEP17 ratio was calculated. For each probe, signal counts greater than 10 were considered innumerable and scored as 10. Cases were considered positive for amplification of Her-2/neu if the Her-2/CEP17 ratio was greater than or equal to 2.0, according to the manufacturer’s instructions.

Cases also were hybridized with the Abbott-Vysis Smith-Magenis assay probe set. These include the SMS probe for the Smith-Magenis syndrome critical region at 17p11.2 (encompassing genes SMS, THRA, and RARA) and labeled with SpectrumOrange and the RARA probe for retinoic acid receptor at 17q21.2 (encompassing GRB7, MKN51, SHGC-I46999, THRA, and RARA exons 2-6, labeled with SpectrumGreen). Details of deparaffinization and hybridization are as in the preceding text. Sections were not available to test case 3.

Immunohistochemical analysis for Her-2/neu protein expression was performed with one of the FDA-approved assay kits, following manufacturer’s instructions exactly.
Cases 1, 2, 6, and 7 were evaluated with the Ventana PATHWAY kit on a Benchmark XT stainer (Ventana), and cases 3, 4, and 5 were stained with the DAKO HercepTest on a DAKO Autostainer. Staining results were scored on a scale of 0, 1+, 2+, and 3+, again following respective kit instructions exactly.

Results

In our clinical practice, we observed several Her-2/neu FISH assays of carcinoma specimens showing a very high copy number of CEP17 (D17Z1) chromosome 17 centromere control signals, unaccounted for by simple chromosome 17 aneusomy. To study such cases in detail, we searched the files of Stanford University Medical Center Cytogenetics Laboratory for Her-2/neu FISH assays with aberrant CEP17 signals and identified 6 cases with greater than 125 signals per 25 cells (5/cell) and a Her-2/CEP17 ratio of 1.0 or less. These 6 cases were derived from 858 assays performed (0.7%). We identified an additional case from the Cytogenetics Laboratory at OHSU. Six cases were intermediate- to high-grade breast carcinomas, and 1 was a high-grade ovarian carcinoma with papillary serous features. All 6 tested cases were negative for hormone receptors ER and PR. Clinical features of the study cases are given in Table 1.

Two cases demonstrated amplification of CEP17, with fewer numbers of Her-2/neu signals (cases 1 and 2) Table 2, Image 1A, and Image 1D, using the standard Her-2/neu FISH assay probes in the PathVysion FDA-approved assay, Her-2/neu, and CEP17 (D17Z1, as chromosome 17 “control” probe). Thus, the Her-2/CEP17 ratio in each of these cases was very low (0.34 and 0.37), with an absolute number of Her-2/neu signals per nucleus ranging from 1.8 to 2.8. The remaining 5 cases (cases 3-7) showed high signal counts for Her-2/neu and CEP17 probes, usually with clusters of innumerable red and green signals in each tumor cell nucleus. The formal Her-2/CEP17 ratio score in each of these cases was approximately 1 (Table 2) Image 1G, even though the number of Her-2/neu signals per nucleus is consistent with amplification (>10 per nucleus).

We sought to further characterize the nature of the apparent CEP17 amplification in these cases by applying FISH probes to other loci on chromosome 17. The Smith-Magenis assay probe set (Abbott-Vysis), designed for detection of the Smith-Magenis microdeletion syndrome, includes probes for SMS and RARA. The RARA probe hybridizes with RARA and neighboring genes at 17q21.2 (labeled with SpectrumGreen), telomeric to Her-2/neu on the long arm of chromosome 17. Further, the SMS probe target sequences are at 17p11.2 (labeled with SpectrumOrange). These additional probes allowed further characterization of chromosome 17 copy number and calculation of Her-2/RARA and Her-2/SMS ratios.

Case 1 demonstrated more than 150 SMS signals per 25 cells, with a diploid RARA count. The Her-2/RARA ratio was normal, but the Her-2/SMS ratio was abnormally low. Thus, there was amplification of CEP17 and SMS but neither RARA nor Her-2/neu on the long arm of 17 (Table 2, Figure 1). For case 2, the SMS/RARA probes were consistent with chromosome 17 polysomy, with greater than 2 signals per cell for RARA and SMS (3.45 and 3 copies per cell, respectively). The Her-2/RARA and Her-2/SMS ratios were each close to 1.0, providing a measure of the actual Her-2/chromosome 17 ratio. Thus, case 2 has a small amplicon involving CEP17 but not involving other tested loci (Table 2, Figure 1).

Cases 4 and 5 had normal complements of SMS and RARA signals, indicating an amplicon encompassing Her-2/neu and CEP17 but not RARA or SMS. The Her-2/chromosome 17 ratio, as derived from either the Her-2/RARA or Her-2/SMS ratio, was markedly elevated in each case, reflecting Her-2/neu gene amplification (>5.55, Table 2, Figure 1).

Table 1
Clinical Features of CEP17-Amplified Cases

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Primary Site</th>
<th>Grade*</th>
<th>Size (cm)</th>
<th>Nodal Status</th>
<th>Receptor Status</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Estrogen</td>
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<tr>
<td>1</td>
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<td>III</td>
<td>2.1</td>
<td>– (0/3)</td>
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<tr>
<td>2</td>
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<td>+ (25/35)</td>
<td>–</td>
</tr>
<tr>
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<td>NA</td>
<td>NA</td>
<td>ND</td>
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<tr>
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<td>2.1</td>
<td>– (0/7)</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>Breast</td>
<td>III</td>
<td>2.7</td>
<td>+ (2/7)</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>Ovary</td>
<td>High grade</td>
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<td>NA</td>
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<tr>
<td>7</td>
<td>Breast</td>
<td>II</td>
<td>&gt;4†</td>
<td>+†</td>
<td>–</td>
</tr>
</tbody>
</table>

NA, not available; ND, not done; –, negative (<5% positive nuclei); +, positive.
* Modified Nottingham grade.
† Based on clinical and radiologic assessment.
These additional probes revealed further chromosome 17 aberrations in cases 6 and 7. Case 6 had slightly increased numbers of signals for SMS and RARA, again compatible with underlying chromosome 17 polysomy (Table 2). For case 6, the Her-2/RARA ratio was slightly less than 2, whereas the Her-2/SMS ratio was clearly elevated (2.90, Table 2). Case 7 had low SMS signals, suggestive of monosomy 17. However, there was apparent amplification of RARA [Image 1H], indicating a large amplicon encompassing Her-2/neu and RARA. In this case, the Her-2/SMS ratio was most indicative of the Her-2/chromosome 17 ratio (8.62, Table 2).

We next correlated the FISH results with Her-2/neu protein expression as assayed by immunohistochemical analysis. Two cases were negative for protein expression (cases 1 and 2) [Image 1C and Image 1F], whereas the remainder of the cases were strongly positive (3+) for Her-2/neu by immunohistochemical analysis (Table 2). The cases with negative immunohistochemical staining were cases with a low number of Her-2/neu signals despite CEP17 amplification. Cases with amplification of CEP17 and Her-2/neu demonstrated strong protein expression at the cell membrane (Table 2) [Image 1I].

**Image 1** Fluorescence in situ hybridization (FISH) and immunohistochemical studies on CEP17-amplified cases. A, (Case 1) Amplified CEP17 (green) and nearly normal numbers of Her-2/neu signals (red). B, (Case 1) Amplified Smith-Magenis syndrome (SMS; red) and normal retinoic acid receptor (RARA) count (green). C, (Case 1) Negative PATHWAY Her-2/neu immunohistochemical result (score, 0). D, (Case 2) Low Her-2/neu signal counts (red) and numerous CEP17 signals (green). E, (Case 2) Polysomy of SMS (red) and RARA (green) signals. F, (Case 2) Negative PATHWAY Her-2/neu immunohistochemical result (score, 0).
Discussion

Robust methods, rigorous quality control, and careful interpretation are required to perform assays to address prognosis and to appropriately predict those patients who will benefit from targeted therapies. This holds true for trastuzumab therapy in breast carcinoma because the treatment is costly and is cardiotoxic in a subset of patients.12-14 Considerable controversy exists regarding the most appropriate testing algorithm for assessment of Her-2/neu status, given the availability of immunohistochemical and FISH assays. Recent data yield an approximately 95% concordance between these assays when performed in experienced reference laboratories, on par with interlaboratory immunohistochemical or interlaboratory FISH concordance.25-28 Current standards indicate that cases scored as 2+ by Her-2/neu immunohistochemical

Table 2
FISH and Immunohistochemical Results

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<td>3+</td>
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<td>&gt;208</td>
<td>1.20</td>
<td>8.62</td>
<td>3+</td>
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</table>

FISH, fluorescence in situ hybridization; ND, not done; RARA, retinoic acid receptor; SMS, Smith-Magenis syndrome.

* For FISH enumeration, more than 10 signals per cell were counted as 10.
analysis should have a reflex confirmatory FISH assay performed; of those, only FISH+ patients are eligible for trastuzumab therapy. Some laboratories perform FISH primarily, and it is unclear how often confirmatory immunohistochemical analysis is performed to resolve cases with atypical FISH patterns.

We identified CEP17 amplification in a series of consecutive Her-2/neu FISH assays. We further investigated the nature of the chromosome 17 amplicon with FISH probes to additional loci (SMS 17p11.2, RARA 17q21.2) and with Her-2/neu immunohistochemical analysis. The use of alternative chromosome 17 probes, SMS and RARA, allows an Her-2/chromosome 17 ratio to be derived, providing an alternative FISH ratio score in cases with a complex CEP17 pattern. Whether cases with amplified CEP17 and amplified Her-2/neu constitute some of the immunohistochemically 3+ positive but FISH negative cases in the literature that may respond to trastuzumab therapy is unclear.11,29,30

Based on results of all 3 assays, CEP17-amplified cases fell into 2 groups. Of 7 study cases, 2 had an unusually low Her-2/CEP17 ratio because of a CEP17 count greater than 125. Thus, the amplified portion of chromosome 17 did not involve the Her-2/neu locus, although the SMS/RARA probes showed that 1 case had a large amplicon involving CEP17 and SMS. These probes also suggested chromosome 17 polysomy in case 2. Cases in this first group were negative for Her-2/neu protein overexpression.

Five cases had apparent amplification of Her-2/neu and CEP17 on initial FISH testing, yielding a ratio of 1.0. This ratio is within normal limits (<2.0); simply reporting the Her-2/CEP17 ratio would not indicate Her-2/neu amplification and may deny targeted therapy. However, all of these cases demonstrated overexpression of Her-2/neu by immunohistochemical analysis. SMS/RARA probes revealed chromosome 17 copy number, and we found that the Her-2/RARA or Her-2/SMS ratio was a better indication of the Her-2/chromosome 17 ratio and was consistent with Her-2/neu amplification in each case. Deletion of the SMS or RARA target loci may account for a shifted Her-2/SMS or Her-2/RARA ratio. However, the cases reported herein had markedly elevated Her-2/neu signal counts, and most had nearly normal SMS or RARA numbers per nucleus (2 per nucleus). Case 7 may have monosomy 17 or deletion of 1 copy of SMS, in addition to a large amplicon including CEP17, Her-2/neu, and RARA.

Further details of the chromosomal content of amplicons are not revealed by these FISH studies (eg, the possibility of complex rearrangements involving those segments). Nevertheless, large amplicons also result in amplification and, perhaps, overexpression of other oncoproteins on chromosome 17. For example, the target sequence of the RARA probe includes the GRB7 locus. MLN64/CABI, PPARBP, topoisomerase IIα, BRC1, and other nearby genes may be affected in such cases.6,8,31

The use of alternative chromosome 17 control probes in Her-2/neu FISH analysis recently was described by Gliem et al24 in abstract form, and our data confirm and extend their findings. They reported 1.23% of 2,855 cases with amplified CEP17 (D17Z1) signals and further tested these cases with a different combination of FISH probes, including Her-2/neu and D17S122 (17p12). They found that 90% of tested cases had an amplified Her-2/D17S122 ratio, and no cases showed amplification of D17S122. However, immunohistochemical correlation was not provided.

Previous reports have described chromosome 17 aneuplody, with dual-color FISH (with chromosome 17 centromere control probe) generally favored over single-color FISH in light of polysomy. Some of these studies also provide brief data alluding to CEP17 amplification. Watts et al18 found aneusomy 17 in 116 (54.2%) of 214 cases and described a maximum CEP17 count of 10.49, without further characterization. Bose et al22 described 24 (32.4%) of 74 cases with aneuploidy 17, with 1 case (1%) showing 7 to 10 CEP17 signals per cell. Press et al28 described 2 (0.08%) of 2,502 cases with Her-2/CEP17 ratios of less than 2.0 but high numbers of Her-2/neu signals per cell, with aggregated Her-2/neu signals, likely representing amplification; however, data on CEP17 were not provided. Wang et al20 found 97 (51.3%) of 189 cases in their selected cohort aneuplastic for chromosome 17, including 10 cases with CEP17 of more than 3.76 per cell. They found concordance between immunohistochemical results and Her-2/CEP17 ratios was maintained, and they concluded there was little influence of chromosome 17 copy number on Her-2/neu expression. In contrast, Ma et al33 reported 377 (42.2%) of 893 polysomic for chromosome 17, with 65 cases (7.3%) of “high polysomy” (>3.75 signals per cell). They found a trend toward increased protein expression with polysomy. Likewise, Varshney et al21 reported 71 (10.3%) of 687 cases with polysomy 17, with 19 cases (2.8%) with high polysomy, defined as CEP17 of more than 4 per cell. It is interesting that cases in the high polysomy cohort with an Her-2/CEP17 ratio less than 2 were identified with negative immunohistochemical results (3 cases) or with positive immunohistochemical results (3+, 6 cases). Although further details are not provided, it is likely that these cases may be similar to cases in our study. We speculate that their cases without protein overexpression may have only CEP17 amplification without Her-2/neu amplification, and their cases with Her-2/neu protein overexpression may have large amplicons encompassing CEP17 and Her-2/neu. Likewise, Hofmann et al29 describe 3 (1.0%) of 302 patients with FISH−, immunohistochemically 3+ positive tumors who responded to trastuzumab therapy and noted that two specimens showed CEP17 of more than 9 per nucleus.
We recommend reporting raw FISH data, including number of cells counted, CEP17 signals, Her-2/neu signals, and the calculated Her-2/CEP17 ratio for routine cases. In cases with aberrant signal patterns such those reported herein, we recommend describing the pattern in a detailed comment. Further evaluating such cases with additional FISH probes targeted at other chromosome 17 loci may be helpful to allow the ratio of Her-2/neu to chromosome 17 copy number to be calculated correctly. Our data also indicate that confirmatory (reflex) immunohistochemical analysis in cases with a complex FISH pattern may add important, clinically relevant information.

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References


