Commentary: Can Circulating HER-2 Extracellular Domain Predict Response to Trastuzumab in HER-2–Negative Breast Cancer?

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Human epidermal growth factor receptor 2 (HER-2) is one of four members of the type I family of tyrosine kinase growth factor receptors. Other members of this family include the epidermal growth factor receptor (EGFR, HER-1), HER-3, and HER-4. These proteins are localized to the cell membrane. Their structure includes an intracellular cytoplasmic domain that exhibits tyrosine kinase activity (except HER-3), a transmembrane domain, and an extracellular domain (ECD). The ECDs of EGFR, HER-3, and HER-4 contain binding sites for multiple ligands. No ligand has been identified for HER-2. Phosphorylation of HER proteins results in activation of critical signal transduction pathways involved in mammalian cell growth. In cancer cells, amplification or otherwise overexpression of HER-2 has been associated with unregulated cell proliferation, invasion, and metastases.

The HER-2 gene is amplified in 20%–25% of invasive breast cancers. Survival rates are worse in patients whose tumors carry the HER-2 gene amplification than in patients whose tumors express normal levels of HER-2. Expression of the truncated form of HER-2 has been associated with yet a worse prognosis compared with expression of the whole HER-2 protein. The HER-2 gene copy number can be determined by fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH). For FISH assays using chromosome 17 (CEP17) as a control, a HER-2/CEP17 ratio >2.2 is considered positive. For FISH assays that do not include CEP17 as a control, at least six copies of the HER-2 gene should be identified for a tumor to be considered HER-2 positive. A tumor is considered HER-2 positive using immunohistochemistry (IHC) if at least 30% of the cells exhibit complete membrane staining. All patients with breast cancer should have their tumors tested for HER-2 expression by either IHC or FISH/CISH to determine eligibility for HER-2–directed therapy [1].

The initial clinical trials of trastuzumab monoclonal antibody therapy (Herceptin®; Genentech, South San Francisco, CA) relied on IHC testing of HER-2 expression in breast cancer tissue using the antibodies 4D5 and CB11. Based on retrospective analyses of archived tissue from patients treated with trastuzumab in clinical trials, the U.S. Food and Drug Administration approved several IHC and FISH assays for selecting breast cancer patients for HER-2–targeted therapy. Although FISH is highly accurate and more reproducible than IHC, both assays are commonly used in the clinic. All laboratories offering HER-2 testing for patient care should follow the guidelines published by the American Society of Clinical Oncology and the College of American Pathologists [1]. It is hoped that these guidelines will improve the accuracy of HER-2 testing in breast cancer and allow proper patient selection for HER-2–targeted therapy.

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Circulating levels of HER-2 ECD can be detected in the serum of breast cancer patients using a commercially available enzyme-linked immunosorbent assay (Bayer, Tarrytown, NY). However, the clinical utility of the serum HER-2 ECD assay is controversial. Some studies found no correlation between HER-2 ECD level and the response rate and/or time to progression in the metastatic setting [2], while other studies showed that a serum HER-2 ECD level >15 ng/ml correlates with a low response rate and short disease-free survival interval in patients with metastatic breast cancer treated with endocrine therapy and chemotherapy. Another potential use of the HER-2 ECD tumor marker is monitoring response to therapy in the metastatic setting. For example, a decline in serum HER-2 ECD levels in the first few weeks after initiation of trastuzumab-based therapy results in a longer disease-free survival interval in patients with HER-2–positive metastatic breast cancer [3]. However, no prospective studies have compared the HER-2 tissue-based and serum-based assays. In addition, it is unclear whether HER-2 ECD is a better marker than cancer antigen 27.29 for patients undergoing HER-2–directed therapy.

In clinical practice, HER-2 status is often assessed in primary breast tumors, and this information is used to make therapeutic decisions in the metastatic setting. One of the limitations of this approach is the archival nature of the available tissue, usually processed months or years before the patient develops distant metastases. The concordance between HER-2 expression in primary tumors and distant metastases is in the range of 80%–94% [4–6]. Discordant cases may be a result of clonal selection or the upregulation of HER-2 during the metastatic process. Meng et al. [7] reported a discordance in HER-2 gene amplification between primary tumor and circulating tumor cells (CTCs) in nine patients with metastatic breast cancer whose primary tumors were HER-2 negative by FISH. Four of these patients were treated with trastuzumab-based chemotherapy, and three achieved objective responses. However, the HER-2 status of the metastatic deposits was unknown, and more data are needed regarding the correlation of HER-2 expression between metastatic tissue and CTCs. Lipton et al. [8] conducted a randomized trial of tamoxifen versus letrozole, and reported elevated HER-2 ECD levels in 28% of patients at baseline. Interestingly, 62 of 240 (26%) patients who were initially HER-2 negative (<15 ng/ml) were found to have elevated circulating HER-2 ECD levels (>15 ng/ml) at the time of progression [8]. These data suggest that HER-2 status is not always conserved during the metastatic process.

If elevated HER-2 ECD levels in the serum reflect activation of the HER-2 pathway in metastatic tumors, measuring HER-2 ECD in the serum of metastatic breast cancer patients would be a great tool to guide therapy. The study reported by Ardavanis et al. [9] in this issue of the journal builds on the hypothesis that elevated circulating HER-2 ECD levels can predict response to HER-2–directed therapy. Twenty-two patients with HER-2–negative metastatic breast cancer were selected for trastuzumab plus a taxane chemotherapy if their serum HER-2 ECD level was >15 ng/ml. All patients had received anthracycline- and taxane-based regimens. The authors reported minor responses and disease stability in 73% of patients, with a median time to progression of 6.5 months. Although objective partial responses were not observed, disease stability is meaningful in this population. However, the sample size of this clinical trial is very small, and it is unclear what was the contribution of the taxane versus that of the combination of the taxane and trastuzumab. Paclitaxel and docetaxel have been shown to produce objective responses and stable disease in patients with metastatic breast cancer independently of the HER-2 status of the primary tumors [10].

Seidman et al. [11] evaluated the potential role of trastuzumab and weekly paclitaxel in patients with metastatic breast cancer whose tumors were HER-2 negative. The hypothesis was that low levels of HER-2 expression might be sufficient to provide a synergistic interaction between paclitaxel and trastuzumab. The response rate was significantly higher in patients with HER-2–overexpressing tumors, but nonetheless, responses and stable disease were also observed in the HER-2–negative patients. The study reported by Ardavanis et al. [9] would be stronger if they had rebiopsied the metastatic tumors to evaluate the correlation between circulating HER-2 ECD and HER-2 overexpression in metastatic breast cancer tissue. Another limitation of this study is the lack of information regarding the timing of HER-2 ECD status. It is possible that the HER-2 ECD level was elevated prior to the development of metastases. A prospective longitudinal study would be helpful to determine when HER-2 ECD elevation occurs in this setting. If HER-2 ECD levels correlate with tumor burden and the metastatic deposit does not exhibit HER-2 gene amplification or HER-2 protein overexpression, this would limit the predictive role of serum HER-2 ECD as a marker of response to HER-2–targeted therapy. On the other hand, a strong correlation between metastatic tissue and serum HER-2 status would support the clinical utility of the serum HER-2 ECD assay for selecting HER-2–directed therapy.

Additional areas of research include the utility of circulating HER-2 ECD in patients whose tumors express a truncated form of HER-2, and in patients treated with lapatinib (Tykerb®; Glaxo Smithkline, Research Triangle Park, NC). In a phase III randomized clinical trial of capecitabine versus capecitabine...
plus lapatinib in patients with HER-2–overexpressing metastatic breast cancer, an elevated HER-2 ECD level at baseline was associated with a short progression-free survival time in patients treated with capecitabine alone. However, HER-2 ECD levels were not predictive of clinical outcome in patients receiving capecitabine and lapatinib [12].

Additional studies are needed to establish the predictive role of HER-2 ECD levels in patients with metastatic breast cancer, particularly if the primary tumors are known to be HER-2 negative. Whenever possible, future studies should include biopsies of metastatic sites to assess HER-2 status and evaluate correlations between tissue and serum testing prospectively. Only then we will be certain that the metastatic clone is dependent on HER-2 for proliferation in the metastatic setting. In that situation, a real-time, minimally invasive blood test such as the HER-2 ECD assay would be clinically useful and an important addition to the management of HER-2–positive breast cancer.

REFERENCES