Is Circulating HER-2 More Than Just a Tumor Marker?

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HER2/neu (also known as neu and as c-erbB-2) is a proto-oncogene of the EGF receptor family of receptor tyrosine kinases (1). HER2/neu encodes a 185,000 transmembrane glycoprotein receptor (HER2, or c-erbB-2) that has partial homology with the other members of the EGF receptor family, and which also includes the EGF receptor (also called HER1), HER3, and HER4. These receptors are composed of an extracellular binding domain, a transmembrane lipophilic segment, and an intracellular protein tyrosine kinase domain with a regulatory carboxyl terminal segment (2). HER2 is overexpressed in 25–30% of breast cancers and its overexpression is associated with a high risk of relapse and death (3). ECD/HER-2 can be released by proteolytic cleavage from the full-length HER2 receptor and detected in the serum of patients.

A humanized antibody directed against the extracellular domain of HER2 has shown clinical activity against HER2-overexpressing breast tumors and has been recently approved for clinical use given alone or in combination with chemotherapy (4–6). Taking these data into consideration, tissue HER2 determination in breast cancer by either immuno-histochemistry or fluorescence in situ hybridization has become increasingly important to provide optimal care to patients with breast cancer (7). The issues remain which of the available methods to determine HER2 overexpression/amplification may be used and whether a plasma-based assay may have a role in the clinic. Levels of circulating ECD/HER-2 are easily detectable in the serum of breast cancer patients, and the Food and Drug Administration has recently approved an ELISA-based HER-2 serum test for use in the follow-up and monitoring of patients with metastatic breast cancer (Bayer Diagnostics, Tarrytown, NY). Over the last years, the measurement of serum ECD/HER-2 levels in patients with breast cancer has been suggested as useful for several clinical applications. These include: the monitoring of women with metastatic breast cancer to aid in patient management; detecting the early appearance of recurrent breast cancer; predicting response to hormonal therapy or chemotherapy; and the selection patients for trastuzumab therapy and the monitoring of response to trastuzumab (8, 9).

In this regard what does the study by Hayes et al. (10) add to our current knowledge? In this study, 242 patients who were enrolled in Cancer and Leukemia Group B (CALGB) prospective therapeutic trials for metastatic breast cancer were assayed for circulating ECD/HER-2 using a commercially available sandwich enzyme immunoassay (10). In their study, elevated ECD/HER-2 levels were observed in 37% of patients and were associated with a shorter overall survival. However, in a multivariate analysis, ECD/HER-2 did not independently correlate with survival. Furthermore, ECD/HER-2 levels were not predictive for time to progression and for response to megestrol acetate or chemotherapy, including a subgroup of patients treated with an anthracycline-containing regimen. The authors concluded appropriately that, like most other circulating tumor markers, circulating levels of ECD/HER-2 are most likely associated with a high tumor burden, and that their utility may be restricted to monitoring the clinical course in patients undergoing therapy.

Is there more to ECD/HER-2 than just another marker of tumor burden? The answer is probably yes. This notion stems from the very nature of ECD/HER-2 generation and release from the tumor cells into the serum. A large body of experiments with cultured cells indicate that transmembrane, full-length HER2 undergoes a proteolytic event that results in the release of the soluble ECD/HER-2 fragment and, concomitantly, in the production of an amino-terminally truncated, cell-associated, HER2 fragment that contains the kinase domain (designated as HER2 p95 because of its molecular weight) with potentially enhanced signaling activity (11–14). It is tempting to speculate that the adverse prognosis observed in patients with high levels of ECD/HER-2 may be related, at least in part, to the fact that it should reflect a concomitant increase of truncated, signaling-competent, HER2 p95. Studies measuring serum ECD/HER-2 and tumor HER2 p95 are needed to fully support this possibility. As examples of the signaling activity of truncated receptors, it has been shown that the cleavage of HER4, a receptor of the same family that HER2, or the TrkA neurotrophin receptor, produces active tyrosine kinase fragments that resemble the activated full-length receptors (15, 16). These results suggest that the extracellular domains of these receptors prevent spontaneous activation of the intracellular kinase domain. Conceivably, ligand-binding or ectodomain cleavage might counteract this inhibitory effect on the kinase domain. This hypothesis is strengthened by studies showing that an engineered deletion of the ECD/HER-2 markedly increases the tyrosine kinase activity and transforms efficiency of the resulting NH2-terminally truncated HER2 protein (17). In support of the in vivo signaling activity of the truncated HER2 p95 fragment, we have found that it is phosphorylated in human breast cancer tumors (14). In addition, the level of HER2 p95 in primary breast tumors is associated with the presence of lymph node metastases, whereas the level of full-length HER2 did not.

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2 The abbreviations used are: EGF, epidermal growth factor; ECD/HER-2, extracellular domain of HER2.
show such an association (12). Hence, these data support a role of HER2 cleavage in human breast cancer progression. In a complementary fashion, the study by Hayes et al. (10) reports a positive correlation between high serum ECD/HER-2 with poor prognosis and visceral metastasis. Because these findings support that ECD/HER-2 plays a role as a marker of an aggressive breast cancer biology, it is warranted to address in future studies the question of whether we can improve the prognostic value of tissue HER2 protein expression or HER2 gene copy number by adding the information of serum ECD/HER-2 levels.

Current data indicate that patients with breast tumors overexpressing HER2 commonly have high levels of serum ECD/HER-2 (4, 5, 18–20). On the basis of this association, additional studies are needed to assess, in the population of breast cancer patients with known tissue HER2 overexpression/amplification, whether serum ECD/HER-2 levels might be better serum markers to monitor tumor relapse than others commonly used, such as CA15–3 or CEA, as suggested in a recent study (18). However, there are cases with high levels of ECD/HER-2 in the absence of HER2 tissue overexpression and vice versa. These discrepancies again might be explained by the regulated process of HER2 cleavage. In this respect, we have shown that the cleavage of HER2 is a highly regulated, metalloprotease-dependent, event, and that breast cancer cells have the HER2 cleavage machinery ready to act on HER2 well beyond their basal activity (13, 14, 21). There are diverse mechanisms that can activate this machinery (i.e., phosphorylation/dephosphorylation, metalloprotease activation, and possibly expression of erbB ligands), and which may have a role in vivo. Therefore, it seems likely that breast tumors may have different levels of these activators of HER2 cleavage, which presumably may lead to variations in serum ECD/HER-2 for a given level of tissue HER2 expression. Hence, serum ECD/HER-2 may reflect, in part, the activation state of the shedding machinery that acts on HER2, instead of being solely a measure of HER2 expression and tumor burden. It will be necessary first to identify the key metalloprotease(s) involved in HER2 cleavage to study this hypothesis in clinical breast cancer samples.

HER2 cleavage may also provide an opportunity for therapeutic intervention. Interestingly, the monoclonal antibody trastuzumab appears to have a direct inhibitory effect on basal and induced HER-2 cleavage, likely attributable to antibody binding to the receptor ectodomain in a way that may hide the cleavage site from the protease responsible for HER2 shedding (14). It is attractive to hypothesize that this inhibition of HER2 cleavage by trastuzumab may have therapeutic value by preventing the formation of the potentially deleterious truncated HER-2 p95 fragments. Other approaches may include the use of matrix metalloprotease inhibitors, which could prevent receptor cleavage, or HER tyrosine kinase inhibitors, which could revert the constitutive activation of the membrane-bound truncated receptor that occurs upon shedding of the extracellular domain.

In closing, what is the clinical utility of determining ECD/HER-2 in the serum of breast cancer patients? The study by Hayes et al. (10) indicates that serum HER-2/ECD is not a predictive factor for response to either hormonal agents or to chemotherapy including anthracyclines, but it is a prognostic factor in breast carcinoma. If basally elevated, serum ECD/HER-2 may be a very useful tool in monitoring early and overall response to therapy, including trastuzumab (19, 20). Likewise, rising ECD/HER-2 levels may be an early indication of disease recurrence or progression. In addition, because there is a correlation between ECD/HER-2 levels and HER-2 expression in the tumor, one might consider selecting patients for trastuzumab therapy on the basis of high ECD/HER-2 levels, if tissue is not available. Finally, elevated ECD/HER-2 levels may reflect a subgroup of tumors with a higher level of HER-2 cleavage and shedding. This subgroup of tumors may have a more aggressive clinical course and, as mentioned, could be specially suited for targeted therapies such as trastuzumab, matrix metalloprotease inhibitors, and receptor tyrosine kinase inhibitors. Therefore, there is strong evidence to support that ECD/HER-2 is not just another tumor marker but, rather, a biological indicator of a distinct subgroup of HER-2-overexpressing breast tumors.

References


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