Editorial

Predicting Response to Herceptin Therapy

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The activation of cellular oncogenes plays an important role in the development of cancer. An important member of the oncogene family is the growth factor receptor known as the human epidermal growth factor receptor-2 (HER-2), which is also referred to as HER-2/neu or c-erbB-2. The HER-2/neu oncogene has been localized to chromosome 17q and encodes a transmembrane tyrosine kinase that is expressed on cells of epithelial origin. The full-length glycoprotein has a molecular weight of M, 185,000 (p185). The extracellular domain (ECD) of the receptor protein is heavily glycosylated, has a molecular weight in the M, 95–115,000 range, and is shed into cultured fluids of SKBR-3 cells (1), as well as plasma and serum from normal individuals and patients with breast cancer (2–4).

The ECD of the HER-2/neu receptor is shed by proteolytic cleavage. This cleavage involves metalloproteinase activity and is inhibited by the metalloproteinase inhibitor tissue inhibitor of metalloproteinase-1 but not tissue inhibitor of metalloproteinase-2. The anti-HER-2/neu antibody Herceptin has a direct inhibitory effect on the basal and activated process involved in HER-2/neu cleavage from HER-2/neu-overexpressing breast cancer cells.

Tissue testing for HER-2/neu protein overexpression has been by immunohistochemistry (IHC) and fluorescence in situ hybridization testing for DNA amplification. These methods are subject to differences in methodology between laboratories, variability in operator interpretation, and variation in reagents. Although the fluorescence in situ hybridization technology is reproducible, the major drawback is that the fluorescence in situ hybridization equipment is expensive and not widely available in diagnostic pathology laboratories.

The third method used to quantitate HER-2/neu in plasma or serum is immunoassay. The commercially available ELISA assay for serum HER-2/neu is manufactured by Oncogene Science (Cambridge, MA). This assay uses two monoclonal antibodies, NB-3 and TA-1, to the HER-2/neu ECD. The upper limit of normal for a healthy control population is 15 ng/ml. A review of 24 references used to evaluate ECD levels in primary breast cancer patients revealed that ~18.5% of the 1923 patients had circulating ECD levels above the control cutoff described in each publication. Furthermore, a review of 45 references and 4622 patients with metastatic breast cancer demonstrated that 43% of the patients who had elevated serum HER-2/neu (5).

To date, this ELISA assay for HER-2/neu ECD has not gained widespread clinical usage. The study by Kostler et al. in this issue addresses many of the outstanding questions regarding the serum HER-2/neu assay. First, what is the relation between IHC (usually performed on the primary tumor tissue) and serum HER-2/neu level drawn usually at the time of disease recurrence? These authors find that patients with IHC 3+ tumors had significantly higher baseline ECD values (median = 53.4, range 5.2–6076 ng/ml) than IHC 2+ overexpression (median = 12.1, range 9.3–19.1 ng/ml; P = 0.002). This confirms an earlier report demonstrating a quite good correlation between IHC, fluorescence in situ hybridization, and serum ELISA (6).

A second issue addressed in this study is whether a baseline serum HER-2/neu test gives prognostic information about disease-free interval and overall survival for patients with metastatic breast cancer. Similar to other studies in the literature, Kostler et al. find that in multivariate Cox regression analyses, there was a strong trend toward longer progression-free (P = 0.09) and overall survival (P = 0.06) in patients with higher baseline ECD values.

The final question addressed by Kostler et al. is whether serial serum HER-2/neu determinations can be used to predict responses of Herceptin therapy. Herceptin does not interfere with the performance of the ELISA assay for ECD. Sera was obtained from 55 patients with HER-2/neu-overexpressing metastatic breast cancer immediately before each weekly administration of Herceptin. A fall in serum HER-2/neu ECD as early as day 15 after Herceptin treatment predicted for disease (7–9).

Because of the relatively small sample size in the study by Kostler et al., this study alone will not change clinical practice. However, because of the expense of treatment with Herceptin and number of new therapies to offer patients with metastatic breast cancer, this study should serve to stimulate the performance of a definitive trial to determine whether monitoring of serial serum HER-2/neu ECD values can give the oncologist an early way to accurately predict the subsequent clinical response to Herceptin treatment.

References


