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Recent advances in molecular biology for cancer research have enhanced understanding of cancer biology and also have influenced the therapeutic scheme. Steroid hormone status and its therapeutic application were the hot issue in the field of breast cancer in the 1980s. In the 1990s, the main interest has moved to gene abnormalities that control growth and differentiation. In regard to breast carcinoma, c-erbB2 (HER-2/neu) has been the most extensively studied proto-oncogene by measurement of both gene amplification and c-erbB2 oncoprotein overexpression (1). In the 2000s, the clinical significance of HER-2/neu and validation of HER-2/neu testing have been actively discussed (2).

HER-2/neu oncogene targeted therapy that uses an anti-HER-2/neu monoclonal antibody, Herceptin® (Trastuzumab, Genentech) would be one of the most fruitful results in the field of translational research in recent years. Herceptin is the first oncogene-targeted therapy to be developed for the treatment of metastatic breast cancer that overexpresses HER-2/neu, which is a novel approach that maximizes the translational impact (3). It has had a special meaning that molecular studies at the laboratory table have reached patient’s bedside. In western countries, Herceptin therapy gives survival benefits of notable quality for a substantial portion of patients with breast cancer (3). Several clinical trials are currently testing this therapy in the adjuvant breast cancer setting (4). Recently, incidences of breast cancer have become the first rank among Korean female cancer patients, and Herceptin is going to appear in Korea in this forthcoming June. As in western countries, determination of HER-2/neu oncogene amplification has become a “hot” issue among Korean clinicians and pathologists because it is necessary for the selection of breast cancer patients to receive Herceptin therapy.

In this issue of the Cancer Research and Treatment, Lee et al. published the results of a comparison of polymerase chain reaction (PCR) and immunohistochemistry (IHC) using polyclonal HER-2/neu antibody from Zymed (San Francisco, CA) for evaluation of HER-2/neu in 163 invasive breast cancer patients. In their report, they achieved an excellent concordance (overall 96.3%) between IHC and PCR. They also discussed the advantages and disadvantages of several detection methods for overexpression or amplification of HER-2/neu.

The c-erbB2 (HER-2/neu) proto-oncogene encodes the production of a cell surface receptor protein called p185HER2, or the HER-2 protein or receptor. HER-2 is a 185-kd protein and is a member of the subfamily of structurally related tyrosine kinase receptors (5). It is known to be important in controlling cell growth and division and possibly in transformation to a cancer cell phenotype. Overexpression of receptor protein on the cell membrane is important in malignant transformation (6). Gene amplification and protein overexpression are reported to occur in 25% to 30% of breast carcinomas, especially those that are poorly differentiated, hormone receptor negative, lymph node positive, and flow aneuploid show relatively high proliferation rates (6,7).

Although estrogen receptor/progesterone receptor remain the only well-established predictive markers of responses to endocrine therapy, amplification and overexpression of HER-2 has an emerging role in prognostic and predictive value for hormonal therapy and choice of adjuvant chemotherapy as well as a target for the targeted Herceptin therapy (8). On the basis of current evidence, other biomarkers add little additional information. Although much evidence suggests that amplification and overexpression of HER-2 are more frequent in aggressive breast carcinomas, the results have been contradictory and controversial for more than a decade (6). Many investigators attributed these controversies to method variation of HER-2 detection.

The Need for Quality Control and Validation of HER-2 Testing

With a practical point of view, what would be the most reliable or effective method to detect HER-2/neu abnormality prior to Herceptin therapy? Most practitioners would be interested in this practical issue because accurate assessment of HER-2 status is essential for patient stratification to this new immunotherapeutic modality, Herceptin therapy. False-positive results may lead to wasted resources, false hope and unnecessary exposure to side effects. On the other hand, false-negative results deny patients the chance of potential life-extending therapy. The two main methods of HER-2/neu testing in use in most routine laboratories are immunohistochemistry

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(IHC) and fluorescence in situ hybridization (FISH) on formalin-fixed, paraffin-embedded, breast cancer tissue. There is no single, universally accepted method and the plethora of testing and interpretative protocols has confounded the issue of clinical correlation of HER-2 status with outcome and patient selection for therapy. The current consensus in the literature is leaning towards FISH because of its high sensitivity, specificity, and reproducibility. However, the use of FISH as a routine test in most diagnostic laboratories is not yet a reality mainly due to cost and to technical and manpower constraints (9,10). In this regard, IHC is by default the preferred choice in many routine laboratories, in spite of lack of quality assurance (9). Conventional immunohistochemical HER-2 overexpression is simple and is easily done by routine pathologic work, but is not reliable for false-positive results. It has been reported to 80% of maximal sensitivity in formalin-fixed tissues (6). We have also experienced the same. What makes the discrepancies between HER-2 results by IHC? IHC results can vary substantially because of multiple factors, including time to fixation, duration of fixation, processing, antigen-retrieval, staining procedure, and staining interpretation (11).

To overcome such limitations, Genentech (the manufacturer of Herceptin) and Dako have collaborated to develop a qualified anti-HER2 immunohistochemical system (kit) to select patients appropriate for treatment with Herceptin. The HercepTest™ (DAKO, Carpinteria, CA, USA) presented a semiquantitative guideline for HER-2/neu immunohistochemistry. The kit (HercepTest™) received Federal Food and Drug Administration approval for Herceptin in the United States (12). It has advantages for objective and reproducible results compared to conventional IHC. Recently a good concordance between FISH and the HercepTest was reported by Paik et al. (98 of 104 cases in agreement), however, it still remains false-positive in category “2+”, compared to FISH (4). An association with FISH is confirmed in strongly positive (3+) HER-2/neu expression by the HercepTest (4,13). By performing both assays, quality can be cross-validated (4). I hope that such cross validation could result in standardization by simple IHC for routine daily practice. According to our experience of the HercepTest™ for the past two years in 600 invasive breast carcinomas in the Korea Cancer Center Hospital, the HercepTest™ is easy to stain and interpret for routine pathological work with consistent staining quality. In my personal opinion, the HercepTest™ can serve as the guideline for HER-2 determination until consensus for an ideal gold standard is reached.

To reduce the practical limitations of FISH for routine pathological work, a new modification of in situ hybridization, the chromogenic in situ hybridization (CISH), has recently been evaluated. CISH enables detection of HER-2/neu gene copies with conventional peroxidase reaction and has the merit of using conventional bright-field microscopy in evaluation (14). Some reports suggest that CISH could be a useful alternative for determination of HER-2/neu amplification in paraffin-embedded tumor samples, especially for confirming ambiguous immunohistochemical staining results (14~16).

Is Herceptin Possible as a Therapeutic Target in Gastric Cancer?

The prognostic and therapeutic value of HER-2 has been shown primarily in breast cancer. However, the HER-2/neu is overexpressed in diverse human cancers and HER-2 overexpression has been implicated to be of prognostic value in gastric cancer (17). Im et al., in this issue of the Cancer Research and Treatment, reported the prognostic significance of the overexpression of HER-2/neu in Korean gastric carcinomas and suggested the possible use of HER-2 as a therapeutic target in gastric cancer. In their report, overexpression of HER-2/neu was detected in 54% of advanced gastric carcinomas by IHC. As described in Im et al.’s report, gastric carcinoma is the second leading cause of cancer deaths in Korea and advanced stage gastric cancer is generally considered incurable. In this regard, HER-2/neu could be a promising therapeutic target for incurable advanced stage gastric cancer. More approaches are needed to expand the targeted therapy to more cancers in addition to breast cancer.

Universal standardization of testing methods for HER-2/neu status determination, together with further clinical studies on the correlation of each method with outcome and response to therapy, will aid in the identification of the ideal method for stratifying patients with breast cancer or gastric cancer into prognostic and optimal therapeutic groups.

REFERENCES

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