MELBOURNE PATHOLOGY

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HERCEPTIN (HER2) TESTING UPDATE

OCTOBER 2006

insight

Trastuzumab (Herceptin), a monoclonal antibody, is an exciting new drug used in the treatment of HER2-positive breast cancer. The HER2 protein is a transmembrane glycoprotein with tyrosine kinase activity, related to epidermal growth factor receptor. These receptors respond to circulating growth factors, increasing cell proliferation. Some 20-30 percent of breast cancers have increased numbers of copies of the HER2 gene (amplification), resulting in increased expression of the HER2 protein on the cell surface membrane. Herceptin acts by degrading the HER2 protein or by facilitiating antibody-dependent cytotoxicity by host lymphocytes.

There is considerable excitement about Herceptin which has been shown to reduce the recurrence rate in HER2-positive advanced breast cancer (after adjuvant or neoadjuvant chemotherapy), and also in early stage HER2-positive breast cancer. A recent trial showed a significant reduction (46 percent) in the recurrence rate in women with early stage HER2-positive breast cancer[1]. The drug can only be administered intravenously and is expensive, and should only be used in cases where it is likely to work i.e. in tumours that definitely show HER2 amplification. HER2 gene amplification can be detected immunohistochemically by staining for the overexpressed HER2 protein on the cell membrane. At Melbourne Pathology all breast carcinomas are stained for HER2 protein, and given a score from 0 to 3+. All those tumours with strong (3+) membranous staining; approximately 25 percent of tumours with moderate (2+) staining; and virtually none of those with weak (1+) or negative (0) staining, have HER2 amplification. After stratification by immunohistochemical staining in our laboratory, all cases with an indeterminate or equivocal result (score 2+) are sent interstate for confirmatory fluorescent in-situ hybridisation (FISH testing). Approximately 25 percent of HER2 equivocal (2+) cases will show HER2 gene amplification on FISH testing and therefore possibly be eligible for Herceptin therapy.

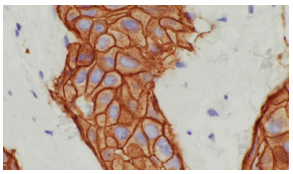

Figure 1: Immunohistochemistry for HER2 showing strong (3+) staining of the greatly increased HER2 receptor protein present on the tumour cell membranes.

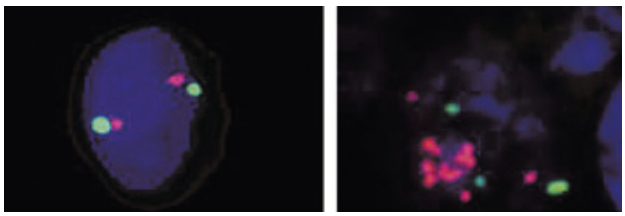

Figure 2: FISH test. The normal cell on the left shows one HER2 gene (pink dot) for each chromosome (depicted by the green dots). The cancer cell on the right shows clusters of pink dots indicating HER2 gene amplification. This results in the increased HER-2 receptor protein expression seen above in Fig. 1.

In Australia the Federal Government has funded Herceptin therapy for patients with late stage HER2 positive breast cancer since 2001. Without this subsidy, treatment costs approximately $60,000 per year. In light of clinical trials showing improved survival and decreased recurrence rates in patients with early (non-metastatic) HER2 breast cancer treated with Herceptin, the Pharmaceutical Benefits Advisory Committee (PBAC) has recently made a recommendation to the Government that Herceptin therapy be made available on the Pharmaceutical Benefits Scheme (PBS) to these early stage patients as well.

NOTE: In late August the Federal Government approved PBS listing of Herceptin for treatment of patients with HER2–positive early stage breast cancer, effective 1 October 2006.

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Footnote: 1. N Engl J Med - 2005 Oct 20: 353 (16): 1659-72.*Trastuzumab after adjucant chemotherapy in HER2-positive breast cancer.*