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E18. How important is c-erb B2 or HER-2/neu when deciding on which therapy?

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The expression of HER-2/neu (ErbB-2) is without doubt predictive for the response of breast tumours to the antibody trastuzumab. With regard to chemotherapy and endocrine therapy the pattern is not so clear cut. There are increasing data that appear to indicate HER-2/neu is associated with a reduced sensitivity to tamoxifen or alkylating agents and an enhanced sensitivity to anthracyclines. However, it is not completely clear whether protein overexpression or DNA amplification is the more appropriate measure, when HER-2/neu status is used for predictive purposes. Further, data derived from few existing studies are not always consistent.

There is some evidence that HER-2/neu-positive tumours are less responsive to tamoxifen therapy, although the mechanism of this tamoxifen resistance is not well understood. The first randomised trial giving evidence of an association of HER-2/neu with tamoxifen resistance was the Italian Gruppo Universitario Natoletano-Trial (GUN) [1] that has been updated recently. In this trial, 433 breast cancer patients were randomised to receive either two years of adjuvant tamoxifen treatment or no treatment. Although the final analysis showed a significant benefit for the tamoxifen-arm, a subset analysis revealed that patients with HER-2/neu-positive tumours did not benefit from the tamoxifen treatment.

A large study comparing different endocrine therapies was published by Ellis and colleagues [2]. In this randomised, neoadjuvant, double-blinded trial, 278 patients that had received either tamoxifen or the aromatase inhibitor, letrozole, underwent core-needle biopsies to asses their HER-2/neu (ErbB-2) and ErbB-1 tumour status. The response rate to letrozole was superior to tamoxifen (60% *vs*. 41% P=0.004). It has to be emphasised that this difference was due to a remarkable higher response rate in those patients with ErbB-1- and HER-2/neu (ErbB-2)-positive tumours (88% for letrozole *vs.* 21% for tamoxifen, P=0.0004). The difference in response rates for ErbB-1- and HER-2/neu (ErbB'-negative tumours was not statistically significant (54% for letrozole *vs*. 42% for tamoxifen, P=0.078). A possible explanation suggested by the author was that tamoxifen resistance can be overcome by an efficient estrogen deprivation therapy. Recently reported data from the Immediate Preoperative Arimidex tamoxifen or Combined with Tamoxifen (IMPACT) trial on the aromatase inhibitor, anastrozole, adds supporting evidence for this theory [3].

The study from Ellis and colleagues [2] showed another remarkable result: the superiority of letrozole over tamoxifen was most marked in tumours that were weakly ER-positive. The aromatase inhibitor presented a response rate of 30% in tumours with an Allred Score of 3–5, while no tumour scoring in this group responded to tamoxifen.

Recent data presented by Syratos and colleagues [4] indicates that HER-2/neu expression is associated with lower oestrogen (ER) and progesterone receptor (PR) levels. There was a significant relationship between HER-2/neu-positivity and the degree of ER-positivity, as determined by quantitative measurement in fmol/mg. Tumours that were HER-2/neu-positive showed lower quantitative ER levels compared with HER-2/neu-negative tumours, and the same difference was observed for high-HER-2/neu overexpressers compared with low-HER-2/neu overexpressers. Similar results were presented by Konecny and colleagues [5] in an even larger clinical cohort.

If there is a quantitative inverse relationship between HER-2/neu expression and ER levels on one hand and a correlation between the response to tamoxifen and the absolute ER levels on the other, this could explain the partial tamoxifen resistance of HER-2/neu-positive tumours and the superiority of aromatase inhibitors in this

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subset of patients. This data indicates that quantitative measurement of the ER could not only be a more appropriate way to predict the response to endocrine treatment, but a predictor for the kind of treatment as well. Meanwhile the question of whether or not HER-2/neu (ErbB-2) tumour tissue measurements are useful for selection of the most efficacious endocrine therapy could become redundant in the near future by the fact that aromatase inhibitors are emerging as the first the choice endocrine therapy for hormone receptor-positive breast cancer patients in the metastatic, neoadjuvant and adjuvant settings. This underlines the importance of HER-2/neu (ErbB-2) determination in tumour tissues collected from patients treated in large ongoing endocrine therapy trials, like Arimidex, tamoxifen, alone or in combination (ATAC), Tamoxifen and Exemestan Adjuvant Multicenter trial (TEAM) and the Breast International Group/Femara Tamoxifen Trial (BIG FEMTA), as it might be our last chance to confirm the role of HER-2/neu (ErbB-2) as a predictive factor for specific endocrine therapies.

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