The state of HER-2 status

This editorial comments on the manuscript reported by Bergqvist et al. [1] who have investigated real-time PCR (RT-PCR) and microarray-based RNA expression (RNA-EP) as alternative strategies to immunohistochemistry (IHC) and in situ hybridization (ISH) for HER-2 testing in breast cancer patients. Bergqvist et al. [1] have compared the performance of ‘standard’ and ‘new’ HER-2 testing tools in a series of ~250 primary breast tumors. Moreover, they have correlated clinical outcomes (relapse-free, breast cancer-related, and overall survival) with HER-2 scores evaluated by the investigated techniques. Bergqvist et al. [1] have to be congratulated for the significant amount of work that has been done and for exhaustively reporting the results of their study.

This editorial will attempt to address two definite questions related to HER-2 testing: (i) in which clinical situation HER-2 testing results are of capital importance for patient’s management? (ii) are new HER-2 testing technologies required to better assist clinicians in the decision-making process?

There are four different clinical scenarios in which HER-2 testing results have or might have a role in the clinical management of breast cancer patients.

The identification of patient candidates for anti-HER-2 therapies either in the early or in the metastatic setting is by far the most relevant information provided by HER-2 testing of breast cancer samples. Large phase III trials have unequivocally proved the efficacy of anti-HER-2 agents such as trastuzumab and lapatinib in patients carrying HER-2-positive tumors [2–7].

An emerging clinical situation in which HER-2 testing results can provide the clinician with meaningful information is represented by early breast cancer patients carrying hormone receptor and HER-2-positive tumors. In this setting, adjuvant hormonotherapy alone, either with antiestrogens or aromatase inhibitors, might not be the most appropriate treatment option. Preclinical and retrospective clinical studies indicate that these tumors might not be entirely sensitive to hormonal agents [8, 9]. In particular, early results from the trans-anastrazole or tamoxifen alone or in combination (TransATAC) study indicate that in the adjuvant setting HER-2 and hormone receptor-positive breast cancer tends to be less sensitive to both tamoxifen and aromatase inhibitors than HER-2-negative and hormone receptor-positive disease. The magnitude of anastrozole’s superiority over tamoxifen seems to be independent of the primary tumor HER-2 status [9]. Of note, this recent finding contrasts the main conclusions from two previously reported neo-adjuvant studies indicating an increased superiority of aromatase inhibitors over tamoxifen in the presence of HER-2 and hormone receptor-positive disease [10, 11]. Of note, the two neo-adjuvant studies correlated HER-2 status with objective response rates to neo-adjuvant hormonotherapy [10, 11], while in the TransATAC study, disease-free survival was the main clinical outcome correlated with the primary tumor HER-2 status [9]. This difference between TransATAC and the two neo-adjuvant studies might explain the apparent discordance. Based on these data, a few courses of adjuvant chemotherapy preceding the start of hormonotherapy might be appropriate in hormone receptor and HER-2-positive early breast cancer, particularly, if in the presence of other factors, indicating increased sensitivity to chemotherapy such as hyperproliferation [12, 13].

The two other clinical scenarios in which HER-2 testing results could assist the clinician in the decision-making process are in my opinion more controversial. HER-2 positivity has repeatedly been indicated as an adverse prognostic factor in early breast cancer patients [14]. A pure prognostic factor indicates prognosis at any time during the patient’s follow-up, while HER-2 positivity seems to be a good predictor of early recurrence (i.e. within 2–3 years from breast cancer surgery) [15]. There is no substantial evidence that HER-2-positive patients who are disease free 5 years after breast cancer surgery are still at an increased risk of relapse when compared with HER-2-negative patients [14]. Conversely, largely accepted prognostic factors such as nodal status and tumor size can provide a prognostic characterization at any time during the patient’s follow-up [16]. HER-2 and hormonal receptors tend to define different breast cancer subclasses, each with a peculiar risk of disease relapse over time and with different degrees of sensitivity to hormonal and cytotoxic agents [15–19].

Markers such as hormone receptors and HER-2 contribute to define the individual tumor’s biological profile and provide guidance on the treatment type to be used (i.e. hormonal therapy, cytotoxics, biotherapies, combination treatment). Pure prognostic factors such as tumor size and nodal status should not play a role in the selection of the treatment type, while they should indicate the ‘level of intensity’ of a given treatment type selected on the basis of the individual tumor’s biological profile. Nevertheless, it has to be recognized that the clinician can be faced with controversial situations (i.e. biologically aggressive tumors with extremely favorable prognostic markers or, vice versa, biologically ‘differentiated’ tumors associated with adverse prognostic factors).

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The last controversial area in which HER-2 testing could provide the clinician with clinically meaningful data is the use of anthracycline-based adjuvant therapy in HER-2-positive breast cancer patients. Despite the fact that different retrospective studies have indicated that only HER-2-positive breast cancer patients derive substantial benefit from anthracycline-based adjuvant therapies [20], a growing set of data are indicating that HER-2 could only be a surrogate marker of anthracycline’s sensitivity because of the topoisoerase II α gene amplification observed in approximately one-third of HER-2 amplified tumors and rarely reported in HER-2 nonamplified breast cancer [21]. In addition, data on topoisoerase II α protein seem to indicate that protein overexpression predicts increased sensitivity to anthracyclines [22–24] and that protein overexpression is reported in HER-2-positive as well as in HER-2-negative tumors independently of the topoisoerase II α gene status [25–27]. These data have certainly contributed to the reconsideration of HER-2’s role as a predictive marker of anthracyclines activity in breast cancer patients.

The second question that the present editorial attempts to address is whether or not new HER-2 testing technologies are needed. The answer to this question is ‘definitely yes’, assuming that the new test provides the clinician with more relevant information than standard tests. The identification of HER-2-positive tumors is certainly crucial in order to identify patient candidates for anti-HER-2 therapies. The new HER-2 test should be more reliable than the currently available tests to carefully select patients eligible for anti-HER-2 therapies. Figure 1 reports the design of an ‘ideal’ study validating a new HER-2 testing technology in patients receiving anti-HER-2 therapies. If the use of the new test ameliorates the selection criteria for anti-HER-2 treatments and leads to an improvement in the clinical activity of anti-HER-2 compounds, then the new test has fulfilled the main requirement and it can become a standard.

The study by Bergqvist et al. [1] discussed in the present editorial cannot evaluate the performance of RT-PCR and RNA-EP in terms of predicting the response to anti-HER-2 therapies because patients from this study were not treated with anti-HER-2 compounds. The indication that HER-2-positive patients by RT-PCR and RNA-EP might have a worse long-term prognosis than HER-2-positive patients by standard tests does not seem to be a strong enough evidence to consider the new tests as an upcoming standard [1]. In fact, the present study indicates, as previously discussed in this editorial, that most if not all of the adverse prognostic significance associated with HER-2 positivity is due to the increased risk of early relapses. Five-year hazard ratios for relapse-free survival were 2.2 and 2.4 and 10-year hazard ratios went down to 1.9 and 1.8 when HER-2 positivity was confirmed by RT-PCR and RNA-EP, respectively. This indicates that if hazard ratios by time periods would have been calculated, hazard ratios for the time period ‘5–10 years’ would have likely lost most of their clinical and statistical significance.

Moreover, as the authors point out, RT-PCR and RNA-EP are certainly less widespread and feasible techniques than IHC and ISH. This is relevant for a diagnostic test that is nowadays routinely carried out in a large number of pathology departments worldwide.

In summary, it is felt that new HER-2 tests might be helpful in providing the clinician with relevant information, in particular, for a more accurate use of anti-HER-2 compounds.

The available evidence does not support the use of RT-PCR and RNA-EP as alternative or complementary tests to currently available HER-2 diagnostic tools.

There are other important issues related to the HER-2 testing field. Among these, improvement in HER-2 scores reproducibility between different laboratories is a high priority, as recently highlighted by an American Society of Clinical Oncology/College of American Pathologists panel [28]. Reproducibility studies indicate that ~20% of HER-2 assays carried out at the treatment site’s pathology department are incorrect when the same specimen is reevaluated in a high-volume central laboratory [29–32].

There are additional research themes. The identification of molecular markers complementing HER-2 scores with the aim to better define the profile of anti-HER-2 compound sensitive tumors is certainly a relevant research area. Different events seem to play a role in the onset of clinical resistance to anti-HER-2 compounds. Among these, activation of the insulin-like growth factor-1 pathway, phosphate and tensin homolog deficiency, phosphoinositide 3-kinase gene mutations, compensatory signaling from other HER family members, and polymorphism of the Fc receptor have been indicated as potential markers of resistance [33]. Ongoing clinical studies will likely clarify the role of these markers in predicting the likelihood of response of HER-2-positive tumors to anti-HER-2 therapies.

An additional theme currently under investigation is the clinical significance of chromosome 17 polysomy in relationship to the activity of anti-HER-2 therapies. It has been reported that most of the IHC HER-2-positive (3+) and FISH-negative tumors carry chromosome 17 polysomy [34]. Large phase III clinical trials that have established anti-HER-2 therapies as a new standard in HER-2-positive breast cancer might help to define the predictive value of chromosome 17.
polyosmoly as far as the clinical activity of anti-HER-2 compounds is concerned. These studies might reveal that tumors carrying high levels of HER2 protein in the absence of gene amplification might also derive some benefit from HER2-targeting therapies.

In conclusion, after many years of research focusing on HER-2 and its significance in breast cancer biology, clinical behavior, and medical treatment, and despite substantial progress that has been done in this field, we have to agree that the HER-2 research area is still evolving and that it will likely continue to impact on our current view of breast cancer biology and treatment.

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