Receptor-based predictors of response in breast cancer

"Further biomarkers are needed if we are to truly realize the potential for improving our prognostic and predictive tools in the treatment of breast cancer."

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Breast cancer remains the most common malignancy in women and mortality rates are falling, but are we really making inroads into the treatment of this complex and heterogeneous disease? Decision making regarding chemotherapy relies on a predictable but often flawed set of criteria, which oncologists have used for the last 20 years – axillary lymph node status, tumor size, lymphovascular invasion, grade and hormone receptor status. There is little doubt that with the advent of new biological and targeted treatments and the development of new molecular techniques, we are still failing to clearly identify those patients who will benefit from chemotherapy, whilst on the other hand heavily overtreating individuals who may derive little benefit from systemic therapy. Improved tools are required to predict response to treatment in breast cancer.

It is over 30 years since growth receptors were first identified and their expression in breast cancer still correctly plays a pivotal role in treatment decisions. Evaluating the expression of hormone receptors and *HER2* expression may now be routine, but what information does this provide us with in regards to the likelihood of response to treatment, and what new biomarkers can be used to further improve our treatment selections?

The estrogen receptor (ER) allows us to predict, at least to some extent, the response of breast cancer to endocrine treatment. Patients with tumors that are also strongly positive for the progesterone receptor (PgR) have the highest likelihood of response [1]. We now know that ER and/or PgR expression is an independent prognostic factor in breast cancer [2]. However, in terms of benefit from chemotherapy, it appears that ER-negative tumors tend to respond better to chemotherapy, rather than ER-positive tumors. Studies have also shown that the likelihood of achieving a pathological complete response (pCR) with primary chemotherapy, a good surrogate for long-term survival in the neoadjuvant setting, is also significantly higher in ER-negative tumors [3]. Thus, patients who have ER-negative cancers likely derive the most benefit from adjuvant chemotherapy.

Overexpression of HER2 is observed in 20–30% of breast cancers, and this has been associated with more aggressive tumors. At least two different genetic mechanisms can lead to increased *HER2* copy number – gene amplification and aneuploidy, where a change in the number of extra copies of chromosome 17 (polysomy 17) is seen [4]. Polysomy 17-positive tumors, which lack *HER2* gene amplification, are pathologically indistinguishable from HER2-negative tumors, and although they have extra copies of *HER2,* they are very different from tumors in which the *HER2* gene is amplified, and may not respond to HER2-targeted therapies.

We can use *HER2* expression as a predictor of response to chemotherapy. Some studies have shown that patients who have *HER2*-positive tumors will benefit from an anthracycline-containing chemotherapy regimen, although the exact mechanism for this remains unclear. There is close proximity of the *HER2* gene to the *TOP2A* gene located on chromosome 17q, and topoisomerase II is known to be a target of the anthracyclines, amongst other proteins [5]. A number of studies have suggested that deletion or overamplification of *TOP2A,* perhaps closely associated with coamplification of *HER2,* leads to a worse prognosis but greater response to anthracycline-containing regimens. Therefore, these are potentially the patients that we should be identifying as requiring aggressive treatment with an anthracycline-containing regimen.

Conversely, HER2 positivity may also be associated with a benefit from treatment with paclitaxel. A study involving 1500 women with

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node-positive breast cancer demonstrated a significant interaction between HER2 status and the addition of adjuvant paclitaxel in patients who had received four cycles of doxorubicin plus cyclophosphamide. This interaction was associated with a hazard ratio for recurrence of 0.59 ($p = 0.01$) [6]. This was independent of ER status: no such benefit was seen with HER2-negative, ER-positive breast cancers.

HER2 overamplification also raises the issue about the use of endocrine treatment. Whilst the debate continues about sequential or extended endocrine treatment in ER-positive patients, is tamoxifen really redundant in HER2-positive patients? Data from the P24 trial comparing neoadjuvant letrozole with tamoxifen demonstrated that in the neoadjuvant setting the response of HER2-positive tumors to tamoxifen was significantly lower than that of HER2-negative tumors – 88 versus 21% ($p = 0.0004$) [7]. Similar results were seen in the neoadjuvant Immediate Preoperative Anastrozole, Tamoxifen, or Combined With Tamoxifen (IMPACT) trial, where a response rate of 58% was observed in the anastrozole arm compared with 22% for tamoxifen in HER2-positive tumors. However these data were not statistically significant, as the analysis was underpowered due to small numbers of patients [8]. There is cross-talk between ER and growth factor receptors, with cytoplasmic ER functioning as a growth receptor ligand, activating HER2 tyrosine kinase activity [9]. As these two receptor systems have the ability to activate each other, combined targeting of both receptors appears to be an attractive therapeutic option.

What of some of the newer receptors identified – will they provide useful markers in the future for response to treatment, particularly targeted treatments? Studies have shown that the EGF receptor (EGFR/HER1) is overexpressed in 16–48% of breast cancers, depending on how it is measured [10]. Targeting EGFR remains an attractive therapeutic option. This includes the use of monoclonal antibodies such as cetuximab and small-molecule tyrosine kinase inhibitors, such as gefitinib and erlotinib. However, studies have shown that the presence of EGFR *per se* is a poor marker of response, and trials investigating the use of both gefitinib and erlotinib in breast cancer have been disappointing. What has emerged, particularly in the treatment of non-small-cell lung cancer, is the observation that specific mutations in the EGFR tyrosine kinase domain may in fact predict response to EGFR inhibitors. The discovery of missense and deletion mutations may lead to a higher affinity of EGFR for gefitinib, and thus lead to a better response to the drug [11]. However, mutations have not been found here in breast cancer, and as expression of EGFR does not equate to a response to EGFR inhibition, the therapeutic options may be limited. Results with lapatinib in breast cancer have been more encouraging [12]. Lapatinib, a dual tyrosine kinase inhibitor, targets both EGFR and HER2, and a number of trials are underway investigating it in EGFR-positive HER2-negative disease to further understand the role of the EGFR.

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Invasive breast cancers that overexpress VEGF have a worse clinical outcome and are often resistant to both hormone therapy and chemotherapy [13]. Bevacizumab has been shown to have activity in advanced breast cancer – its addition to paclitaxel improved response rates from 14% for paclitaxel alone to 28% with the combination [14]. In advanced breast cancer it is likely that a number of proangiogenic factors are in operation, and targeting a single pathway is a fruitless operation. VEGF overexpression appears to be an early step in breast cancer progression and is seen frequently in ductal carcinoma *in situ*, long before tumor invasion [15]. By the time patients have developed metastatic disease, the benefits of bevacizumab may be lost, and we are now undertaking trials in early-stage disease to truly assess the benefit of bevacizumab and its role in the adjuvant setting. Sunitinib and sorafenib, both tyrosine kinase inhibitors, can also target the VEGF receptor, but once again trials have generally involved heavily pretreated patients with advanced disease, perhaps masking the true benefit of these novel drugs. Studies continue to elucidate whether angiogenic markers in tumors may be of prognostic and predictive value in the future.

Just as the expression of certain receptors can guide our treatments, so too can their absence. A number of different pathological subclasses of breast cancer have been identified based on gene-expression profiles. Of particular interest are triple-negative breast cancers – such as breast cancers that do not express ER, PgR or

HER2. This subtype comprises approximately 15–20% of breast cancers, and the majority of triple-negative cancers have basal-like expression profiles, expressing cytokeratins that are normally found in the cell layer lying closest to the epithelial basement membrane [16]. Similar markers are also expressed in BRCA1-associated cancers. Tissue microarray studies have shown a high rate of EGFR overexpression in these triple-negative cancers [17], and c-kit expression is also higher. Interestingly, these tumors are sensitive to chemotherapy, and the pCR rate may be higher in these cancers than some of the other subtypes. However, they have a high risk of relapse in contrast to other cases with pCRs. Evidence is now emerging that these cancers may be more sensitive to DNA-damaging agents, such as platinum-based regimens, as these tumors have deficient DNA-repair mechanisms. As EGFR is also present in approximately 60% of these tumors, combining platinum-based treatment with EGFR inhibitors, such as gefitinib, could be an attractive therapeutic option.

In the future, gene-expression profiling may aid our decision-making when trying to identify particular patients who will most benefit from treatment. However, 'prognosis profiling' carries with it its own limitations. OncotypeDx™ (Genomic Health, Inc., CA, USA), for example, is an assay that includes 16 tumor-related genes and five reference genes that generate a quantitative 'risk of recurrence' score [18]. Care must be taken when using these tools to help us decide about treatment, as the beneficial data they provide over and above ER, PgR and HER2 may be limited. Many of these assays are based on molecular profiling of a specific group of patients – what may be predictive in premenopausal, ER and lymph-node-negative patients may not apply in a post-menopausal, ER-positive patient. Although useful, there is currently insufficient data and evidence to base our clinical decisions purely on these assays.

Alongside the well established predictive markers such as ER, PgR and HER2, we still require better tools to correctly identify patients that will truly benefit from chemotherapy. Despite recent advances, we are still unable to predict the patients that may respond to treatment, particularly to some of the novel drugs such as EGFR inhibitors and antiangiogenics. Further biomarkers are needed if we are to truly realize the potential for improving our prognostic and predictive tools in the treatment of breast cancer. As we now know that receptors expressed by a tumor may change, we are currently studying those on the surface of circulating tumor cells, obtained in a single blood test, in order to guide our therapeutic strategies [19]. This creates the possibility of treating a patient according to their expression of receptors at that time.

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