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Validated biomarkers: The key to precision treatment in patients with breast cancer

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ABSTRACT

Recent DNA sequencing and gene expression studies have shown that at a molecular level, almost every case of breast cancer is unique and different from other breast cancers. For optimum management therefore, every patient should receive treatment that is guided by the molecular composition of their tumor, i.e., precision treatment. While such a scenario is still some distance into the future, biomarkers are beginning to play an important role in preparing the way for precision treatment. In particular, biomarkers are increasingly being used for predicting patient outcome and informing as to the most appropriate type of systemic therapy to be administered. Mandatory biomarkers for every newly diagnosed case of breast cancer are estrogen receptors and progesterone receptors in selecting patients for endocrine treatment and HER2 for identifying patients likely to benefit from anti-HER2 therapy. Amongst the best validated prognostic biomarker tests are uPA/PAI-1, MammaPrint and Oncotype DX. Although currently, there are no biomarkers available for predicting response to specific forms of chemotherapy, uPA/PAI-1 and Oncotype DX can aid the identification of lymph node-negative patients that are most likely to benefit from adjuvant chemotherapy, in general. In order to accelerate progress towards precision treatment for women with breast cancer, we need additional predictive biomarkers, especially for enhancing the positive predictive value for endocrine and anti-HER2 therapies, as well as biomarkers for predicting response to specific forms of chemotherapy. The ultimate biomarker test for achieving the goal of precision treatment for patients with breast cancer will likely require a combination of gene sequencing and transcriptomic analysis of every patient's tumor.

The traditional approach to treating patients with cancer is often referred to as “trial and error” or “one size fits all” [1]. The consequences of this approach may include unnecessary treatment in some situations, under-treatment in other situations, low response rates and unnecessary toxicity [1,2]. In contrast to the traditional approach, precision medicine (also known as personalized, individualized or stratified medicine) involves administering treatments that targets the needs of an individual patient on the basis of biology, biomarker expression, phenotypic or psychosocial criteria [3]. Compared to the traditional approach, precision treatment would be expected to increase efficacy, decrease toxicity and ultimately result in a more cost-effective patient management [1,2]. Of all the solid cancers, breast cancer has led the way in introducing precision treatment. This aim of this article is to review the role of biomarkers in this development.

Why we need precision therapy for breast cancer

One of the major insights into tumor biology provided by high throughput technologies such as the modern methods of DNA sequencing and gene expression profiling has been the extent of intertumor heterogeneity at a molecular level, i.e., no 2 individual's tumors at the molecular level appear to be identical. Although patients may share some common mutations, every individual appears to have a different profile of altered genes. Thus, of the hundreds of different genes shown to be mutated in primary invasive breast cancer only 3, i.e., TP53 (p53), PIK3CA and GATA3

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are mutated in more than 10% of cases [4,5]. Most of the remaining genes are altered in <1–2% of patients [4,5].

In addition to this intertumor heterogeneity at the DNA levels, major heterogeneity is also found at the mRNA expression level. Thus, based on gene expression profiling at the mRNA level, several molecular classifications have been proposed for breast cancer [2,6]. One of the most widely described of these molecular classifications separates breast cancers into 4 subgroups, referred to as luminal A, luminal B, HER2-enriched and basal-type. These 4 subgroups exhibit different prognosis and different response to systemic therapies. The key molecular characteristics of the 4 subgroups are summarized in Table 1. These molecular subgroups, especially the basal type, can be further subdivided [7,8].

Since at a molecular level, almost every case of breast cancer appears to be different from all others, theoretically, each patient should have an individualized treatment that matches the molecular abnormality in her tumor. Clearly, at present, this is not practicable but it must be the ultimate aim for the treatment of patients with breast cancer. In order to progress towards that goal, we will need a detailed understanding of the biology/molecular pathology of every case of breast cancer. For practical purposes, the biology of a tumor can potentially be manifested and measured with biomarkers. Biomarkers are thus the key to precision treatment for breast cancer. Biomarkers help with precision treatment in 2 main ways, i.e., by predicting patient outcome and thus identifying the high-risk groups who should receive adjuvant chemotherapy and in selecting the most appropriate therapy for a given patient.

Role of biomarkers in determining patient outcome

Following a diagnosis of breast cancer, the most immediate challenge in patient management, is determination of the aggressiveness of the tumor, i.e., how likely is the formation of a recurrence. Addressing this question is not only informative for prognosis but more importantly, it identifies if there is a need for adjuvant treatment in a given patient. Traditionally, determining patient outcome was based on a series of histopathological and clinical criteria, such as the presence and number of metastatic axillary nodes, tumor size, tumor grade, patient age and patient performance status. While these factors have been used for decades in predicting outcome and guiding treatment, they are clearly inadequate for precision treatment. In particular, these clinical and pathological criteria lack accuracy for determining prognosis in patients with lymph node-negative disease, small tumors (<2 cm) or those with intermediate grade tumors (grade II). This inability of the traditional prognostic factors to provide accurate prognostic information results in many women, especially those with lymph node-negative ER-positive disease, being over-treated with adjuvant chemotherapy [9,10].

Avoiding unnecessary and ineffective adjuvant therapy is thus an important goal in the precision management of patients with newly diagnosed breast cancer. In particular, we need to identify patients with lymph-node negative or low lymph node disease burden that are likely to have such a good outcome that they do not require adjuvant chemotherapy. In such a scenario, these patients can be spared from unnecessary and toxic side effects of chemotherapy, resulting in a higher quality of life and less costly care. Equally important, we need to identify those patients at increased risk of developing recurrent disease, as these women are likely to benefit from systemic treatment.

Consequently, in recent years, an enormous amount of research has been devoted to the discovery and validation of prognostic biomarkers for breast cancer, especially for the subgroup with lymph node-negative disease [10,11]. Much of this research has focused on multi-parameter biomarker tests, the assumption being that the simultaneous measurement of multiple biomarkers is likely to provide more accurate information than that obtained with a single analyte. Of the multiple prognostic biomarker tests investigated to-date, amongst the best validated for clinical application are uPA/PAI-1, Oncotype DX, MammaPrint, Prosigna and EndoPredict (Table 2). The clinical value of these tests is discussed below.

uPA and PAI-1

Unique among breast cancer prognostic biomarkers, the ability of uPA/PAI-1 to predict patient outcome has been validated in both a pooled analysis of individual patient data [12] and in a prospective randomized trial [13,14], i.e., in 2 level 1 evidence studies. The pooled analysis which contained individual data on 8377 patients from 18 different European Centers showed that uPA and PAI-1 were independent predictors of outcome in women with either lymph node-negative or lymph node-positive disease. Notably, both these biomarkers predicted outcome in patients who received no systemic adjuvant therapy, suggesting that they reflect the underlying tumor biology and tumor natural history.

The independent prognostic impact of uPA/PAI-1 in lymph node-negative patients observed in the above mentioned pooled analysis was confirmed in a multicentre prospective randomized clinical trial, in which biomarker validation was the primary purpose of the trial [13,14]. Ten year analysis of this trial showed that almost half of lymph node-negative patients could be spared from receiving adjuvant chemotherapy, while high risk patients, identified by uPA/PAI-1, were found to benefit from adjuvant chemotherapy. Although tumor grade was also an independent prognostic factor in this study, uPA/PAI-1 was a significant predictor of outcome in patients with the intermediate grade, i.e., grade 2 tumors [14].

Table 1
Characteristics of the subforms of a commonly used molecular classification system for breast cancer. *Basal breast cancers generally have a poor outcome. However, some rare histological forms (medullary, low grade metaplastic and adenoid cystic) tend to have a good outcome. Data summarized from Refs. [1] and [2].

Subtype	Molecular characteristics	Prognosis/Response to therapy
Luminal A	ER-rich, PR-positive, HER2 negative, low grade, low proliferation	Good prognosis, responsive to endocrine therapy
Luminal B	Low ER, PR low or negative, high grade, high proliferation	Compared to luminal A, prognosis is less good, and response to endocrine is lower
HER2-enriched	Overexpression of HER2 gene amplicon	In the absence of anti-HER2 therapy prognosis is poor. If treated with anti-HER2 therapy outcome is substantially improved, i.e., show responsiveness to anti-HER2 therapy
Basal	High levels of keratin 5 and 17. Most (70–80%) lack ER, PR and HER2 but have p53 mutations.	Prognosis is generally poor*, Unresponsive to hormone or anti-HER2 therapy