Breast Cancer Prognostic Markers: Are They Really Addressing the Issues?

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Breast cancer is a contrasting disease with an asymmetric morphology, molecular features, which makes it atypical in response to therapies. Conventionally, prognostic markers in breast cancer is based on the clinico-pathological parameters and detached molecular markers, but on the other hand breast cancer prognosis behaves to some extent asymmetrically in different ethnic groups; although this is a debatable topic, but this situation still exists.

Family history does play a different role in prognosis according to a contemporarily published study where an accumulated number of ER negative & PR negative breast cancer was acclaimed among younger Spanish women who have a family account of the disease [1]. The established/routinely used prognostic markers which are being used by some of the highly respected institutes are ER, PR, Her-2, p53, CD31, Ki-67/PCNA. Trastuzumab is being offered to Her-2 positive patients who will benefit with this monoclonal drug or in other words Her-2 is being performed on a selective group of patients. Whereas ER, PR, p53, CD31, Ki-67/PCNA are being performed on almost every breast cancer patient.

Histologically, the majority of breast cancers (65% to 80%) belong to an ascitic subtype, invasive ductal carcinoma. This communicatively contours the use of type as a prognostic mediator [2]. Therefore, assessment of tumor behavior for any breast cancer case has been based on deltoid parameters: tumor size, lymph node condition, and histological grade. Tumor size is a good prognostic marker for metastasis or otherwise in lymph node negative patients, although patients with small tumors (<1 cm) after the surgical removal are not offered any further treatment, have algorithmically a 12% adventitious of periodicity [3–4]. Lymph node status is still appraised the best prognostic indicator of relapse, but with the commencement of the drugs like tamoxifen and trastuzumab, a more molecular characterization of the tumour is in great demand. There are about 54 drugs which have been approved by the Food and Drug Administration for treatment; so the oncologist thus requires some kind of may be accurate advocacy about the molecular characteristic of the tumour to deal with some precision.

More recently, a battery of four prognostic markers (ER, PR, HER2 and Ki67) has been shown to have a high prognostic impact which could be similar to that of gene expression assays [5]. Some other markers, like serine protease urokinase-type plasminogen activator (uPA) and its inhibitor (plasminogen activator inhibitor type-1;PAI-1) have reached the evidence level by where it can be judged by the American Society for Clinical Oncology as acceptable for clinical use in patients with newly diagnosed node negative breast cancer using an ELISA assay. These assays, although are quantitative, and limited to the use of fresh/frozen tissues. In the case of uPA/PAI-1, a miserly of 300 mg of fresh/frozen breast cancer tissue is needed. Given the fringed availability of frozen tissues in the clinical setting, this heightens a doubt about its exercise in routine endeavor.

Gene assertion profiling assays have assorted breast cancer into five molecular subtypes; luminal A, luminal B, HER2, basal-like, and normal-like [6]. Luminal A (ER+ and Ki67 low) cancers are appeared to adhere the eclipse prognosis; HER2 and basal cancers (also sometimes accredited to as triple negative tumors) have the worst prognosis, and the prognosis for luminal B (ER+ and Ki67 high) cancers is in between. According to this study, rate of proliferation and ER status is vouching the prognosis and therapeutic regime.

Recently, protein biomarkers appraised by reverse phase protein arrays show consequential intra-tumour heterogeneity in breast cancer, and 15 additional proteins have been assayed belonging either to the identical protein family as claimant proteins (EGFR, HER3, HER4, PDGFR and VEGFR) or involved in downstream signaling of the candidate molecules (Akt, ERK, FAK, GSK3b, ILK, Integrin aV, PI3K, p38, PTEN and STAT3) [7]. In another current study, it was acclaimed that many of these proteins are complementary with uPA and PAI-1 assertion in primary breast cancers and might be dictatorial for uPA and PAI-1 accompanied tumor augmentation and metastasis [8]. The expression of uPA was correlated with expression of ER and the Stat3/ERK pathway while PAI-1 was affiliated with Akt signaling and regulation of the HER family. As the activated proteins, the phosphorylated proteins that are frequent appraised include pAkt, p1086EGFR, p1148EGFR, pER, pERK, pGSK3b, pHer2, pHer3, pPDGFR, pp38, pPR, pPTEN, p727STAT3 and p705STAT3.

Contemporarily, a new category analogously ER-a, with a molecular weight of 36 kDa was named as ER-a36. The conceptive 66 kDa ER-a was named ER-a66. ER-a36 escala tamoxifen agonist activity through activation of the membrane-initiated signaling pathways in endometrial cancer, and is involved in de novo and acquired tamoxifen resistance in breast cancer [9].

Tumors are impregnated by macrophages, T and B-lymphocytes, which may abet tumor conception by advancing angiogenesis, amplification along with aggression. In a current analysis, it has been shown that an accumulated CD68 count and CD68/(CD3+CD20) ratio were directly associated with both Matrix metalloproteinases-11 and Tissue inhibitor of metalloproteinase-2 (TIMP-2) assertion by mononuclear inflammatory cells at the tumour centre. In addition, a high CD68/(CD3+CD20) ratio was eloquently affiliated with a higher likelihood of decreased relapse-free survival. Multivariate analysis confessed that CD68/(CD3+CD20) ratio was an alienated factor affiliated with distant relapse-free survival, on account of, CD68/(CD3+CD20) ratio at the invasive front could be aligned with an authoritative prognostic marker.

In a latest study, the author analyzed a kinesin family member 26B (KIF26B) assertion in breast cancer tissues, and analyzed the association between KIF26B expression and clinico-pathological factors to ascertain the amplitude role of KIF26B in breast cancer prognostic
envisioning. There attestation convinced that KIF26B was notably over expressed in breast cancer and could abet as an intensity biomarker of prognosis [10].

I have mentioned here several prognostic indicators, most of which are novel markers and all backed-up by some follow-up and statistical significance. Now the question is which one should be added to the routinely performed suite of markers or they are subjected to the treatment offered to the individual patients based on their current status of disease or the future outcome. According to my understanding none of the studies has even touched to answer this question. Also considering the potential that all these new prognostic biomarkers may have, how many can we test at a given time on a single patient, especially when the patient has to bear the costs, and we are unaware whether we will be able to achieve the required result for that patient. The dilemma is more information and less answer. The reporting guideline provided by the American Society of Clinical Oncology/College of American Pathologists is for Her-2 [11], ER and PR [12] since their expression is associated with trastuzumab and/or tamoxifen treatment. The reporting guidelines for other markers have not been provided so far, and even before that consensus will have to be achieved on which other markers to be used.

References
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