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Review Article

Genomic Advancements in Breast Cancer: Comprehensive Review

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ABSTRACT

Recent advancements in molecular biology has led to revolution in knowledge of breast cancer. Lately there is a swing from clinic pathological attitude to evolving genomic posture. Clinico pathological attitude for estimation of recurrence exploits physical characteristics such as tumor size, histological grade, and number of metastatic axillary lymph nodes. For planning of treatment, it uses IHC for determination of levels of ER/PR receptors and HER2 is determined by IHC or in situ hybridization. On the contrary Genomic concept comprises of study of cluster of genes. These biomarkers can be recognized by using Oncotype Dx a 21 gene set; PAM50 intrinsic subtyping; or by distinguishing favorable versus unfavorable outcome using cDNA microarrays to identify genes i.e. Mamma Print a 70 gene analysis. This information is of immense importance in estimating the risk of recurrence of breast cancer at an early stage and to identify patients who are benefited from chemotherapy.

The genetic signature can forecast whether it will (a) respond to certain medicines or not, (b) metastasize to lymph nodes, and (c) respond to radiation or chemotherapy or newer drugs (d) Also it can estimate the risk of recurrence. We can tailor our treatment in most cases using the detailed molecular knowledge. Some tumors look alike in histological slides; yet by molecular stain, we can identify each tumor in correct manner, allowing us to choose the proper treatment. Spread of tumor is also linked to molecular and genetic knowledge, as size of tumor or histology i.e. classical clinic pathological survey alone cannot predict the course of disease, in breast cancer. Aggressive type of tumor will need a more aggressive treatment, whereas indolent type of tumor will need a more conservative approach. This has led to availability of polymerase chain reaction (PCR) and microarray tests that has profoundly changed the way that oncologists calculate the recurrence risk in early stage breast cancer patients.

Keywords: Breast Cancer, Molecular Subtypes, Genomic Concept.

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INTRODUCTION

Over the past two decades, the molecular dissection of breast cancer has led to revolution in knowledge of breast cancer. Though the initial work up and management of breast cancer is still banking on histopathological and immune histochemical means, but scenario is now shifting from classical clinico pathological attitude towards evolving genomic notion.

As regards the breast cancer is concerned Classical Clinico pathological approach exploits physical characteristics such as tumor size, histological grade, and number of metastatic axillary lymph nodes for assessment and for treatment planning it uses IHC (Immunohistochemistry) for determination of levels of ER/PR receptors & uses IHC/ISH (in situ hybridization) for HER2 determination.

On the contrary Genomic concept comprises of study of cluster of genes. These biomarkers can be recognized by using Oncotype Dx a 21 gene set; PAM50 intrinsic subtyping; or by distinguishing favorable versus unfavorable outcome using cDNA microarrays to identify genes i.e. Mamma Print 70gene analysis. This information is of immense importance in estimating the risk of recurrence of breast cancer at an early stage and to recognize patients who are benefited from chemotherapy. Classical clinico pathological scenario makes use of features viz tumor size, tumor grade, lymph node involvement, and hormone receptor status for prediction of recurrence and to tailor the treatment. The downside of the clinic pathological approach is that it instigates overzealous treatment especially in women with hormone-receptor- positive,

HER2-negative tumors with chemotherapy. This is well evident in Austrian Breast and Colorectal Cancer Study Group trial, ABCSG-12 where in a group of 1800 premenopausal women with Hormone receptor positive (out of which 30% with node positive disease) breast cancer, received adjuvant hormonal therapy alone, and reported 7 yrs. overall survival was 95%. Quite a large number of them if would have been treated in United States might have received chemotherapy fitting to classical clinico pathological approach where nodal status is the main decisive factor for cytotoxic chemotherapy and thus leads to overzealous cytotoxic treatment.[1-2]

GENOMIC CONCEPT - A RECENT APPROACH

Recently developed Genomic concept inculcates calculating prognosis and treatment of breast cancer patients by studying the design of cluster of cancer related genes and their transcripts.

The genetic signature can forecast whether it will (a) respond to certain medicines or not, (b) metastasize to lymph nodes, and (c) respond to radiation or chemotherapy or newer drugs (d) Also it can estimate the risk of recurrence.

We can tailor our treatment in most cases using the detailed molecular knowledge. Some tumors look alike in histological slides; yet by molecular stain, we can identify each tumor in correct manner, allowing us to choose the proper treatment.

Spread of tumor is also linked to molecular and genetic knowledge, as size of tumor or histology i.e. classical clinic pathological survey alone cannot predict the course of disease, especially in breast cancer. Aggressive type of tumor will need a more aggressive treatment, whereas indolent type of tumor will need a more conservative approach.

In this article we review the application of Genomic concept in management of breast cancer.

BREAST CANCER MOLECULAR SUBTYPES-GENOMIC CONCEPT IN BREAST CANCER[3-7]

Breast cancer is a heterogeneous group of diseases. On basis of hormone receptor status and by using traditional IHC techniques breast cancer can be classified it into three-sub groups viz HR positive; Triple negative and HER2/neu positive breast cancer. Each of these above subtypes has distinct features and requires different management strategies. Normal breast tissue comprises of epithelial cells of three types viz luminal or Glandular type; Basal or myoepithelial cells and stem cells.

On the basis of Gene expression profiling and hierarchical clustering there are at least seven major breast cancer molecular subtypes. These include Luminal A, Luminal B, Luminal C, HER2-enriched, basal like, claudin-low and normal breast like.

Luminal Type Breast Cancers Subtype

Luminal like breast cancer derives its name from its similarity to the expression profile of normal luminal breast epithelium.

Luminal A type cancers carry the best prognosis and comprises of about 40% of all breast cancers has overexpression of ER regulated genes, under expression of HER2 gene cluster and under expression of proliferation related genes. They are sensitive to endocrine therapy and less sensitive to cytotoxic chemotherapy in neo adjuvant as well as metastatic setting.[8-10] (Hue et al. 2006; Voduc et al. 2010; Kennecke et al. 2010).

Luminal B breast cancers have much lower expression of ER-related genes, a variable expression of an HER2 cluster of genes, and a relatively higher expression of proliferation-related genes (Voduc et al. 2010). They represent about 20% of breast cancers. Luminal B tumors have also been shown to have genomic instability, and to harbor mutations in *TP53*. Luminal B tumors are associated with a relatively higher risk of recurrence. Luminal A and B tumors are both known to be much less sensitive to cytotoxic chemotherapy, as evidenced by low pathological complete response rates after neoadjuvant chemotherapy. The luminal B subtype is less common than the luminal A subtype, and it carries a poorer prognosis.[11-13]

A third type that is **Luminal C** is also identified that has a different set of genes with unknown function which is a feature they share with Basal like and HER2 subtypes (Sorlie et al 2001). Some of the genes that were identified in Luminal-C include transferrin receptor (CD71), MYB, *nuclear protein* p40, SQLE, and GGH.

Luminal subtype B & C have worse relapse free survival and overall survival, when compared to luminal A (Sorlie et al. 2001).[3]

HER2 Enriched Breast Cancer Subtype

HER2 enriched breast cancer represents 20 to 30% of all breast cancers. They are characterized by over expression of HER2 /*neu* proliferation genes and under expression of luminal clusters.[14] (Perou et al. 2000)

Luminal clusters include luminal cyto keratins (CKs) CK7, CK8, CK18, and CK19, and some of the luminal-associated markers such as human endogenous retrovirus envelope PL1, X-box-binding protein 1, hepatocyte nuclear factor 3, GATA-binding protein 3, Annexin XXXI, and estrogen receptor 1, among others.[14-16]

HER2 enriched tumors are usually, but not always, HER2-positive and ER/PR-negative.

They carry a poor prognosis and have a higher rate of loco regional as well as metastasis to brain, liver, lung compared with luminal A tumor.[4,9,10] (Voduc et al. 2010; Kennecke et al. 2010)

Basal Like Breast Cancer Subtype

Basal like breast cancer subtype derives its name from the fact that it shares gene expression patterns with basal epithelial cells. This subtype represents about 15% of all invasive breast cancers. The gene expression cluster characteristic of basal epithelial cells includes: keratin 5,6, and 17, integrin-β4, laminin, and fatty-acid binding protein 7.[3,14]

They are usually ER-negative, PR-negative, HER2-negative (Triple Negative); CK5/6-positive, and/ or EGFR (HER1)-positive by IHC.[17]

They are considered ER/PR and HER2/*neu* negative ("triple negative") due to low expression of the luminal and HER2 gene clusters.

Triple negative (TN) and Basal-like type are not same and 30% of TN are not basal like.[18] It also shows BRCA1 mutations, increased genomic instability, high expression of the instability, high expression of the proliferation cluster of genes, and a high histologic grade.[19]

Claudin Low Breast Cancer Subtype

This is characterized by high expression of genes associated with epithelial to mesenchymal (EMT) transition. These are (1) cell communication genes, e g chemokine (C-X-C motif) ligand 12; (2) extracellular matrix formation genes, e.g. vimentin and fibroblast growth factor 7 genes, which are involved in extracellular matrix formation; (3) cell differentiation genes, e.g. Krüppel-like factor 2, (4) cell migration genes, e g integrin a5 and moesin; (5)

angiogenesis genes, e.g. vascular endothelial growth factor C, matrix metallopeptidase 9 (MMP-9); (6) immune related genes, e.g. CD79b, CD14, and vav1; and (7) stem-cell like genes, e g CD44+/CD24- and high ALDH1A1.[20] Majority of these have no expression of luminal differentiation markers, and are HER2 and hormone-receptor-negative by IHC, frequently exhibit metaplastic and medullary differentiation, and are often part of the basal intrinsic subgroup.[20]

GENE EXPRESSION PROFILE IN BREAST CANCER

Gene expression profiling is a new expertise that identifies genes whose activity can be used as molecular signature in prediction of prognosis and molding treatment. Genetic material in the form of DNA is transcribed into mRNA, which further gets translated into proteins, which decides cellular behavior.[4,21]

Oligonucleotide arrays, cDNA, and multiplex polymerase chain reaction (PCR) as well as mRNA level technologies have been used to generate molecular signatures.

Marc et al. carried a study in Netherlands cancer institute by using microarray analysis to evaluate 70 gene prognosis profile, and classified a series of 295 consecutive patients with primary breast cancer as having a gene expression signature associated with either a poor prognosis or a good prognosis and concluded that gene expression profile is a more powerful predictor of the outcome of disease in young patients than standard system based on clinical and histologic criteria.

GENOMIC ASSAYS

Predictive or Prognostic

The words prognostic and predictive appear to be identical but there are certain differences. Predictive biomarker recognizes patients who would gain from a specific intervention while Prognostic assay provides information about the outcome of disease independent of the treatment modality adopted. Some biomarkers are both prognostic and predictive such as protein overexpression or gene amplification of HER2.

First genomic biomarker assay was Oncotype Dx which was initially applied on women with hormone receptor positive disease and who were receiving endocrine therapy and thus gives recurrence score for patients on endocrine therapy. On the other hand, Gene signatures comprising PAM 50 and Mamma Print included all subtypes of breast cancer.

Oncotype DX

Oncotype DX is a multiplex, 21-gene, real time, PCR-based assay for assessment of recurrence in women with stages I and II hormone-receptor-positive, lymph-node-negative, invasive breast cancer, and who had tamoxifen for 5 years. This genomic assay was made after selecting a group of genes that was thought to be most relevant to the biology of hormone-receptor breast cancer.

The 21 genes are divided into 2 groups: 16 are cancer related, and 5 are reference genes that serve as internal controls.[22]

Mamma Print

Mamma Print is a 70-gene expression pro le that was initially developed from whole-genome-expression (25,000 genes) arrays of consecutively collected breast cancer specimens from a cohort of women who had undergone definitive surgery only, with no systemic therapy and with known long-term clinical outcomes. The overall approach for developing this prognostic pro le was distinct from that used in the development of the previously discussed Oncotype DX assay, which was derived from a set of 250 preselected candidate genes believed to have prognostic importance in hormone-receptor-positive breast cancer.[23]

PAM 50

Invasive breast cancers can be classified by whole gene arrays into at least 4 major biological “intrinsic” subtypes—referred to as luminal A, luminal B, HER2-enriched, and basal-like—and 3 subtypes that are less used clinically: luminal C, normal like, and claudin-low. These subtypes have been reproducibly identified in the research setting by microarray and RT-PCR. In 2009, Parker et al proposed a 50-gene set, Prediction Analysis of Microarrays (PAM50), for standardizing subtype classification.[24]

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