

Basal-like breast cancer: The road less travelled

Dear readers,

Breast cancer is the most common cancer in women worldwide, more than one million women are affected by this disease.^[1] Breast cancer comprises heterogeneous group of diseases with varied in terms of presentation, morphology, molecular features, clinical behavior and response to therapy. Currently the clinical management and prognosis of breast cancer depends on expression of estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor (Her2neu), which has been proven to provide therapeutic predictive value.

The gene expression microarray based studies have led to the identification of five molecular subtypes of breast cancer; luminal A (ER +ve, PR +ve, Her2neu -ve), luminal B (ER +ve, PR +ve, Her2neu +/-ve), Her2 (ER -ve, PR -ve, Her2neu +ve), normal breast-like (ER -ve, PR -ve, Her2neu -ve, Basal marker negative), and basal like (ER -ve, PR -ve, Her2neu -ve, Basal marker positive). The term basal-like has been referring to myoepithelial cells, which are basally located in the breast glands. Basal-like cancers are heterogeneous category comprising mainly of Infiltrating duct carcinoma- not otherwise specified type. Medullary, atypical medullary, metaplastic, secretory, myoepithelial, and adenoid cystic carcinomas of the breast also show a basal-like phenotype.^[2] It has been demonstrated that these tumors have distinctive clinical presentations, histological features, response to chemotherapy, sites of distant metastasis, recurrence and outcome.

Basal-like breast cancer, shows ER, PR and Her2neu negativity (triple negative tumors) According to gene expression profiling (GEP), 71% of triple-negative tumors showed a basal-like phenotype, and 77% of basal-like tumors showed a triple-negative phenotype.^[3] Both terminology are not synonymous to each other. There is still no internationally accepted, working definition for basal-like breast cancers.

A high proportion of these tumor show dysfunctional BRCA-1 protein.^[4] Immunohistochemical (IHC) expression of TP53 gene mutation, alterations of the pRB and p16INK4a, cyclinEG1/S cell cycle checkpoint are remarkably prevalent in these cancers.^[5] The molecular profiles and clinico-pathologic features overlap between basal-like, triple-negative and BRCA-1-associated cancers.

GEP is the gold standard for the identification of basal-like breast cancer, the use of microarrays is still costly and cumbersome. The panel comprises of surrogate IHC markers (ER, HER2neu, CK5/6, CK14, CK17, and epidermal growth factor receptor [EGFR]) identifies basal-like cancers with 100% specificity and 76% sensitivity. Other markers that have also been used as part of the definition of basal-like cancer include EGFR, C-kit, IMP3, P-cadherin, nestin, osteonectin, vimentin, laminin, caveolins 1 and 2, $\alpha\beta$ -crystallin.^[6]

Basal-like breast cancer represents from 10% to 17% of all breast cancer cases, in the age ranges from 47 to 55 years. Most are younger premenopausal and African/Asian descent than with non-basal tumors. The association between basal tumors and younger age (with higher breast density), the rapid tumor growth rate, low incidence of micro calcification and the lack of association with peritumoral DCIS, other precursor or associated lesions may reflect the low detection rate of basal-like cancer by mammography when compared with other molecular classes.^[7] Clinically, basal-like breast cancer typically presents as a rapidly growing breast mass, sometimes as an “interval breast cancer” diagnosed between annual mammograms.^[8]

On Microscopy, basal-like cancers are usually of high histological grade; 75% to 100% are grade-III. Other important histological features include pushing, non-infiltrative borders of invasion, large zones of geographic or comedo-type necrosis, tissue infarction, hyalinization and fibrosis. Fibrotic focus of greater than 30% of tumor size is associated with a poor prognosis.^[8] Stromal lymphocytic infiltrates, scant stromal content, marked cellular pleomorphism, high nuclear-cytoplasmic ratios, vesicular chromatin, prominent nucleoli, high mitotic indices and frequent apoptotic cells are also seen. Presences of metaplastic elements, in the form of squamous and spindle cells are also seen. Basal-like breast cancers show a higher propensity for visceral metastases to brain and lung, less frequently to axillary lymph nodes, liver and bones. Patients have increased risk for early relapses, particularly higher in the first 3 to 5 years from the time of diagnosis, after which the risk declines drastically. This poor prognosis may be explained by the over expression of EGFR, VEGFR2, and ab-crystallin genes promoting proliferation, angiogenesis, and migration has been shown to correlate with shorter disease-free survival.^[8] Adenoid cystic carcinomas and secretory carcinomas of breast, though fall in Basal group of tumor category, show favorable prognosis. This emphasizes the heterogeneous nature of basal-like carcinomas.

Clinicians have been using anthracycline and taxane based chemotherapy to treat patients with basal-like aggressive breast cancers. In one study, neoadjuvant chemotherapy resulted in complete pathologic response in 45% of basal-like breast cancers compared to 6% of the luminal tumors.^[8] More than 50% of patients still continue

to have residual disease and/or carry a high risk for relapse and death within 5 years of diagnosis.

The BRCA1 mutation-associated group is important to recognize, as Poly ADP ribose polymerase (PARP) inhibitors: olaparib and veliparib, anthracycline or taxane based chemotherapy seem to show good results in this group.

Although no targeted therapy for basal-like breast cancer is currently available, several potential therapeutic targets have been identified in these tumors including EGFR, HER3 and HER4, c-KIT, tyrosine kinase components of the mitogen-activated protein (MAP) kinase pathway, and tyrosine kinase components of the protein kinase B (Akt) pathway.^[9] Bevacizumab, the anti-VEGF antibody, anti-EGFR inhibitor are promising agent in this type of tumor.

To conclude, basal-like breast cancers are the most difficult to treat, largely unresponsive to clinically available targeted therapies, frequently have the worse prognosis, shorter survival and high mortality among breast tumor subtypes. Identification of these tumors in clinical practice may be important. The better understanding of the molecular background of this cancer will help to discover new targeted therapy.

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