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Molecular subtypes and clinicopathological features of breastcancer

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ABSTRACT

Breast cancer is a heterogeneous disease with regard to morphological spectrum, clinical presentation and response to therapy. Based on immunohistochemistry detection of estrogen receptor, progesterone receptor, Her-2 status, proliferation rate and clusters of basal gene expression, breast cancers can be classified into luminal A, luminal B, basal-like/triple negative, and Her-2 positive. It was suggested that there was a close relationship between molecular subtypes and clinicopathological features of breast cancer, as they are very important to predict prognosis and therapeutic implications.

ABSTRAK

Kanker payudara merupakan penyakit yang heterogen dalam spectrum morfologi, manifestasi klinis dan respon terapi. Deteksi imunohistokimiawi dengan marker *estrogen receptor, progesterone receptor*, status Her-2, proliferasi dan ekspresi berbagai kluster gen sel basal, mengelompokkan kanker payudara menjadi berbagai subtype: luminal A, luminal B, basal-like/ triple negative, dan Her-2 positif. Subtipe molecular kanker payudara nampaknya juga berhubungan erat dengan klinik optologis dan sangat penting untuk memprediksi prognosis dan menentukan terapi penderita.

Keywords: molecular subtypes - breast cancer- clinicopathological features - heterogeneity – theraputic implications

INTRODUCTION

Breast cancer is a heterogeneous disease that has different prognoses and responses to therapy despite the similarities in histological type, grade and stage. The heterogeneity of breast cancer cannot be explained only by clinical parameters such as tumor size, lymph node involvement, histological grade, age, or by biomarkers like estrogen receptor (ER), progesterone receptor (PR) and epidermal growth factor receptor 2 (Her-2) which is routinely used in the diagnosis and treatment of patients.[1,2] It is believed that different clinical behaviors of breast cancer are due to molecular differences. A better understanding of breast tumor heterogeneity and the nature of tumor-propagating cells requires delineation of the mammary epithelial subtypes that reside within normal human breast tissue. Therefore, tracing of specific mammary epithelial cells is important to definitely identify cells of origin for the different tumor types.[3]Breast cancer can

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be consistently categorized into subtypes with derivation from the normal basal and luminal mammary epithelial cells.[4,5]

Recent development of high molecular method offers new opportunities to capture the wide range of genomic and biologic variability in breast cancers. The molecular classification of breast cancers using microarray technique is limited to fresh/frozen samples. Therefore, several studies have tried to define immunohistochemical or quantitative real time reverse transcript as polymerase chain reaction (RT-PCR) using formalin-fixed paraffin-embedded samples, for identification of themolecular subtypes.[6]

A pioneer study done by Perou *et al*.[7] using gene-expression signature, classified breast cancers into two main subgroups, namely ER positive and ER negative cancers. The ER positive cancers comprise of the luminal tumors which can be subdivided into at least two distinct subgroups, namely luminal A and luminal B. The ER negative cancers consist of at least three subgroups of cancers, i.e. Her-2 positive, basal-like/triple negative and normal-like cancers. The types of breast cancer that do not fulfill those criteria belong to unclassified cancer.[8,9]

Several studies proved that molecular subtyping of breast cancer has a close relationship with clinicopathological features and is very important to predict clinical outcome and response to therapy. This article is focused on discussing the molecular subtypes and clinicopathological features of breast cancer.

DISCUSSION

Breast cancer, a leading cause of cancer death in women, is recognized to be a molecularly heterogeneous tumor. Histologically, similar tumors may have different prognoses and treatment responses that clearly are due to molecular differences. Molecular profiling, based upon variations in gene expression, has been used to characterize breast cancers beyond the conventional use of grade, histology and immunohistochemical analysis of hormone receptors and Her-2 over-expression.[10] Normal breast ducts are lined by two distinct differentiated cell types, luminal cells lining the apical surface of the duct and myoepithelial cells that reside within the basal layer. Therefore, breast cancer can be categorized into subtypes that are consistent with derivation from the normal basal and luminal mammary epithelial cells.[4,5]

Gene expression studies have identified several distinct breast cancer subtypes. These include two main subtypes of ER positive cancers (luminal A and luminal B) and at least three ER negative cancers (basal-like/ triple negative, Her-2 positive and normal-like). These subtypes are different markedly in prognosis and therapeutic implications. Genes that differentiate these subtypes are called the intrinsic genes and made up of several clusters of genes relating to ER, PR expression, Her-2 expression, proliferation and cluster of basal genes.[6]

The luminal A cancers include 56% ductal and 23% lobular carcinoma, while most (75-89%) of luminal B, basal-like/triple negative and Her-2 positive cancers are ductal carcinoma.[11] In general, the luminal A cancers have the best prognosis, while the luminal B cancers suffer a significantly worse outcome. Both the basal-like/triple negative and Her-2 positive cancer have the worst survival rate, until the era of Her-2 targeting has altered the outcome for the Her-2 subtypes and Her-2 luminal cancers. The luminal A cancers generally require ER inhibitors such as tamoxifen and aromatase inhibitors, which is also a part of the treatment of the luminal B cancers. Chemotherapy is indicated for most

patients with the luminal B, Her-2 positive and basal-like/triple negative, with the addition of trastuzumab I to Her-2 positive cancers.[10] The normal-like breast cancer is rather poorly understood. One of the main characteristics of these cancers is that they consistently cluster together with samples of normal breast and fibroadenomas.[6]

The prevalence of molecular breast cancer subtypes varies among races. A study in Egypt found that luminal A subtype was the most prevalent (41.2%), followed by triple negative subtype (28.5%), then Her-2 subtype (19.4%) and luminal B subtype (13.9%).[12] In Chinese women, the prevalence of luminal A, luminal B, Her-2 and triple negative subtypes were 48.6%, 16.7%, 13.7% and 12.9%, respectively.[13] Among young African-American women, basal-like cancers occurred with higher prevalence compared with luminal cancers.[8] Among breast cancer women in north-east of Morocco, luminal A subtype was more prevalent (53.6%) and associated with favorable clinicpathological characteristics, followed by luminal B (16.4%), Her2-overexpressing (12.6%), basal-like (12.6%) and unclassified subtype (4.9%).[14]

The luminal cancers

The luminal cancers, called luminal A and luminal B, are expressed genes that are also expressed by normal breast luminal epithelial cells cytokeratine 8 and 18. Most of breast cancers (60%) are luminal cancers. The luminal cancer cells look the most like the cells of breast cancers that start in the inner (luminal) cells lining the mammary ducts. The luminal cancers are characterized by expression of ER, PR and other genes associated with ER activation.[10,15]

The luminal A cancers have a greater frequency of small cancer (d" 2cm) and tend to have the best prognosis in comparison to the other breast cancer subtypes.[11] These cancers have a low or moderate tumor grade and only 12-15% of them have p53 mutation, a factor linked with a poorer prognosis.[8] The typical immunohistochemical profiles of luminal type A breast cancers are ER positive and or PR positive, Her-2 negative and low proliferation rate. The recurrence rate of this cancer is 27.8%—significantly lower than that for other subtype. Survival from the time of relapse of these cancers is also longer (median 2.2 years).[2,16]

The luminal B cancers could represent a more aggressive phenotype and are often diagnosed at a younger age than the luminal A ones. The main biological difference between luminal A and B is an increased expression of proliferation genes, such as Ki-67 and cyclin B1 in the luminal B subtype which also expresses EGFR and Her-2. Some researchers classify luminal B tumors in the ER-positive subgroup with poor prognosis.[17,18] Luminal B tumor shave a worse prognosis than luminal A tumors. The bone is still the most common site of recurrence (30%) of this tumor. The survival rate from time of relapse is low (1.6 years).[17]

The treatment of luminal A subgroup of breast cancer is mainly based on third-generation hormonal aromatase inhibitors in postmenopausal patients, selective estrogen receptor modulators (SERMs) like tamoxifen and pure selective regulators of ER like fulvestrant. These cancers were less responsive to chemotheraphy.[2,16]

The luminal B cancers, despite being treated with tamoxifen and aromatase inhibitor, also respond better to neoadjuvant chemotherapy achieving pathological complete response (pCR) in 17% of the luminal B tumors (7% in luminal A), however, this is clearly lower than for the Her-2 and basal-like tumors with values of 36% and 43%, repectively.[19] For luminal B cancers, the panel considers that both anthracyclines and taxanes should be included

in the chemotherapy regimens.[19] For those reasons, treatment of this subtype of breast cancer is currently challenging.

The basal-like/triple negative cancers

The basal-like subtypes are named based on the many gene characteristics of normal breast basal epithelial cells that they express. Most triple negative tumors are basal-like, and most basal-like tumors are triple negative. However, not all triple negative tumors are basal-like tumors and not all basal-like tumors are triple negative. About 15-20% of breast cancers are triple negative or basal-like.[2] Basal-like cancers can occur due to the alteration of BRCA-I gene function, either by mutation or by epigenetic mechanisms. BRCA-1 gene is critical in the DNA repair and its inactivation leads to the accumulation of errors and genetic instability favoring the tumor growth.[20] Clinically, basal-like/triple negative cancers are characterized by their appearance at an early age women, with large tumor size at diagnosis, a high histological grade and a high frequency of lymph node metastasis.[20] Basal-like cancers tend to be breast cancer with a high mitotic index, tumor necrosis, and the pattern of metastatic relapse that are predominantly to the lung, central nervous system and lymph node. These cancers have a higher relapse rate in the first 3 years, despite presenting a high response to chemotherapy.[1] The high rate of p53 mutation in these cancers may explain their aggressiveness and poor prognosis. Therefore, it is critical to find new therapeutic targets and design appropriate treatment strategies.[1]

Basal-like/triple negative cancers are usually treated with some combinations of surgery, radiation therapy and chemotherapy. These tumors cannot be treated with hormone therapies or trastuzumab (Herceptin®) because they are hormone receptor-negative and Her-2 negative. The genes linked to basal-like tumors are not well understood and thus, targeted therapies do not yet exist. However, there are potential targets for future therapies including the EGF receptor, aB-crystalin and cyclin E.[21]

The Her-2 subtype cancers

About 10-15% of breast cancers are Her-2 subtype. They are characterized by low expression of luminal clusters, high expression of the Her-2 gene and other genes associated with the Her-2 pathway and/or Her-2 amplification located in the 17q 12 chromosomes. These tumors also have a high proliferative rate. 75% have a high histological grade and more than 40% have p53 mutation.[19] From clinical point of view, Her-2 type tumors have a fairly poor prognosis and are prone to early recurrence and metastases. Women with Her-2 type tumors appear to be diagnosed at a younger age than those with luminal tumors.[2,22]

A humanized monoclonal anti Her-2 antibody, trastuzumab, is offered for early and advanced breast cancer patients whose tumors have Her-2 3+immunohistochemial expression or Her-2 gene amplification. Novel therapeutic strategies have been proposed, for example monoclonal antibodies that are allegedly more effective in blocking Her-2 heterodimerization (e.g. pertuzumab)[23] and Her-2 tyrosine kinase inhibitors (e.g. lapatinib) in clinical trials.[24] Both Her-2 subtype and the basal-like subtype have a high chemosensitivity with higher response rate than that of luminal tumors, in the neo-adjuvant study.[19]

CONCLUSION

Based on gene expression profiling or immunohistochemical characteristics, breast cancer can be classified into four major subtypes: luminal A, luminal B, Her-2 positive and basal-like/triple negative. Several studies suggest that there is a close relationship between

molecular subtypes and clinicopathological features of breast cancer. Molecular subtyping of breast cancer becomes useful in predicting prognosis, planning treatment and developing new therapies.

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