

Utility of prognostic markers in management of breast cancer

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Abstract

Breast cancer is a disease which is surrounded by mystery. The last century has seen the "invasions" of various biomarkers and their roles have been searched in various trials. The roles of these biomarkers were reviewed by extensive literature search (journals, text books and internet). This article deals with the classification of the available markers, the role of these markers as prognostic and predictive factors and tries to put forward the presently available evidences in order to validate or repute their roles in clinical practice. It could be observed that in spite of tremendous advances in technology, axillary nodal status still remains the single most important factor determining the treatment and outcome.

INTRODUCTION

Breast cancer is the commonest cancer in females worldwide. In spite of the huge research in this area, its behaviour still remains an enigma. Thus, evolution of breast cancer prognosis is at the top of the agenda in breast oncology today. A prognostic factor is defined as any measurement available at the time of diagnosis or surgery that is associated with disease-free survival or overall survival in the absence of systemic therapy. A predictive factor, on the other hand, is any measurement associated with response or lack of it to a particular therapy.

IMPLICATIONS

1. Identification of patients who are prognostically good and thus, local treatment is adequate for them and adjuvant treatment may be cost-ineffective.
2. Identification of patients who are prognostically poor and will thus require more aggressive treatment in addition to conventional treatment.
3. Ascertain which patients are likely or not likely to benefit from specific therapy.
4. Understanding the biological behaviour of the disease so as to develop newer modalities of treatment.

Presently available markers can be classified on the basis of

1. Patient characteristics: age, ethnicity
2. Tumour characteristics: tumour size, axillary lymph nodal status, histological types and pathological character, tumour grade
3. Measures of proliferation: mitotic index, thymidine labelling index, S-phase fraction, Ki-67 staining
4. Steroid receptors and regulators
5. Growth factors and receptors: epidermal growth factor receptor, HER 2/neu
6. Tumour suppressor gene: p53
7. Measures of invasiveness: cathepsin D, plasminogen activators and inhibitors, laminin receptors
8. Angiogenesis

AGE

Most of the trial reports regarding the effect of age and menopausal status on survival are conflicting. Two large trials carefully analyzed the clinical outcomes of young patients with breast cancer and concluded that breast cancer below the age of 35 years is associated with poorer outcome than in older patients.^{1,2} This may be due to different biological character or response to hormonal therapy.

ETHNICITY

Survival after the diagnosis of breast cancer is worse among African-American and Hispanic women than in whites.

TUMOUR SIZE

In patients with node-negative disease, tumour size and histopathological subtypes are the most important parameters in prognosticating the cancer. Most retrospective studies confirm that tumours smaller than one centimeter have excellent prognosis compared to larger tumours. ³ Data from San Antonio suggests a plateau in the risk of recurrence for tumours between three and six centimeters in diameter. Larger tumours behave poorly. We have observed that there seem to be two types of large tumours viz aggressive breast cancers (those with short natural history) and neglected large tumours (having a relatively long and indolent course).

AXILLARY NODAL STATUS

It is the single most important prognostic marker of breast cancer and the major predictive factor regarding treatment planning. Halstead described the axilla as the site of barrier to systemic spread. However, it lost its significance during the Fischerian systemic theory era. The Spectrum theory (2000) once again placed the axilla as the cornerstone of prognosis. Though it is not a barrier to systemic spread, it is the site of host-tumour interaction and rarely, if ever, a systemic metastasis is expected in absence of axillary involvement.

Although most trials stratify breast cancers into three nodal groups (negative nodes, one to three nodes, four or more nodes), several groups have demonstrated a direct relationship between number of nodes involved and clinical outcome. The advent of sentinel lymph node biopsy and evaluation of the isolated nodes have also revolutionized the axillary evaluation. Newer technologies like immunohistochemistry and polymerase chain reaction have led to identification of metastasis in nodes which are negative on histopathology.^{4,5} Controversy surrounds the significance of micrometastasis and its impact on overall survival and selection of therapy. ⁶ It is agreed by most that metastasis less than two millimeter area in a node is probably insignificant. The level and station of nodal involvement also carries prognostic importance. In a series of 1119 patients, Veronesi et al. (1983) (7) showed that when either the axillary or IMC nodes are involved separately, prognosis is similar (Veronesi et al. 1993).

TUMOR GRADE

Tumor grade is said to be a powerful predictor of the course of breast cancer. There are various grading systems. Of them, the Scarff-Bloom-Richardson (SBR) classification is most universally accepted. It comprises degree of differentiation (tubular, glandular or papillary), extent of pleomorphism and mitotic index. The scores of these three items are summed up and categorized as Grade I (well differentiated), Grade II (moderately differentiated) or Grade III (poorly differentiated). Higher grades are likely to have poorer outcome.

HISTOLOGICAL CHARACTER

The pathological characters which carry poor prognosis are:

1. Type: less common histological types (medullary, mucoid, papillary) show better prognosis than common infiltrating carcinomas (ductal, lobular)
2. Presence of extensive in situ carcinoma (EISU)
3. Lympho-vascular permeation
4. Tumor necrosis
5. Mononuclear inflammatory cell reaction.

MEASURES OF PROLIFERATION

The proliferative capacity of the cancer cells should reflect the biological character of a particular tumor. The oldest, easiest and the cheapest way of assessing it is mitotic index. It is expressed as the number of mitoses per high-power field. Expressing the mitotic activity as the number of mitoses divided by the cancer cells eliminates variability in size of the field, cellularity and tumor size. Russo et al. reported an RR of 1.59 and 2.12 for disease recurrence and death, respectively, for patients with higher mitotic grades. ⁸

Thymidine labeling index is a method of counting the number of labeled nuclei on autoradiographed microsections after incubation of the tumor specimen with titrated thymidine. Initially, determination of TLI required fresh tumor specimen. Presently, in-vitro kits are available. The relative risk of relapse based on multivariate analysis of various studies is 2. ⁹ However, its role as a predictive marker is unsettled. The cell kinetics can be divided into G0-G1 consisting of non-dividing (G0) or quiescent (G1) cells, S-phase comprising of cells in synthesis or replicating phase and G2-M phase including cells which are in post-synthetic (G2) and in mitotic (M) state. DNA flow cytometry

performed on fresh tissue, frozen samples, needle aspirates or paraffin-embedded tissues can estimate the DNA ploidy and fraction of cells in S-phase. Most studies clearly support an association between high S-phase fraction and increased risk of recurrence and mortality for patients with both node-positive and node-negative tumors. However, a major limitation is the problem of mixing of stromal elements in the clinical sample. Thus, the measured SPF is highly dependant on the percentage of normal host cells in the sample. Like with TLI, the role of SPF as a predictive marker remains undecided. Ki-67 is an interesting tool for evaluating the proliferative capacity of cancer cells. It is a monoclonal antibody which is specific for a nuclear antigen expressed only in proliferating cells. It is detected by rapid IHC assay, correlates directly with tumor size, grade, vascular invasion and axillary nodal status, and inversely with presence of steroid receptors.¹⁰ However, the prognostic significance of Ki-67 was based mostly on univariate analysis.

STERIOD RECEPTORS

ER and PR status have an established role as predictive markers.¹¹ They can also be used as a prognostic marker.¹² Data from San Antonio and the NSABP indicate that DFS advantage is approximately 10% at 5 years for ER positive tumors.¹³ The role of PR is not well established. It is probably related to overall survival. PR is a measure of intact estrogen response pathway and thus is a better indicator of response to endocrine therapy after disease recurrence.¹⁴

In addition to being a prognostic factor itself, ER positive status is more likely to be found in older women, in well-differentiated tumours, in those with a lower fraction of dividing cells and in diploid ones. ER positive tumours are less likely to exhibit a mutation, loss or amplification of breast cancer related genes (p53, HER2/neu, EGFR).

However, the author has noted a good correlation between ER status and prognosis in the early breast cancer group and the significance is weaker in higher stage disease. Most guidelines take ER status as a risk-defining factor in node-negative patients.

The pS2 gene was identified in human breast cancer cell lines in relation to estrogen.¹⁵ It is located at chromosome 21q. Its exact function is unknown. Some studies have shown that pS2 expression reflects the functional status of ER. It might have both predictive and prognostic significance in primary breast cancer. The evidence is strong

in some univariate and multivariate analysis.

GROWTH FACTORS

a. Epidermal growth factor (also known as cErb-b1)

Thirty-five to sixty percent of breast cancer over-express EGFR. Though many univariate analysis suggest poorer OS and DFS with increasing EGFR status, multivariate analysis could not establish it. Most of the studies suffer from lack of standardization of assay methods, small sample size and short follow-up intervals. However, it remains a promising tool for prognostication.

The role of EGFR as predictive marker is very clear. Tumors over-expressing EGFR are more likely to be ER negative and thus are insensitive to endocrine therapy.

b. HER2/neu (also known as cErb-b2)

HER2/neu is over expressed in comedo, large-cell DCIS, but relatively low levels are found in cribriform and papillary in-situ carcinoma. Ravdin and Chamness summarized the results from 18 studies in invasive breast cancer (each with sample size more than 100 and with at least 3 years follow-up). It was obvious that the promising results of univariate analysis were not reproducible in multivariate analysis. The reviewers concluded that over-expression of HER2/neu as measured by IHC had a weak correlation with DFS but may add to the prediction of OS. Thus, presently there is little support in favor of using HER2/neu as a risk stratification factor in node-negative patients, the group for which prognostication is most important.

The predictive role of it is very promising.¹⁶ Retrospective analysis of patients enrolled in the NSABP B11 study clearly demonstrated that tumors positive for HER2/neu had improved clinical outcome with a doxorubicin-based regime. Most other trials concluded in the same line.

The relationship of HER2/neu and response to endocrine therapy is also interesting. In HER2/neu positive metastatic disease response rates to tamoxifen are lower.¹⁷ In adjuvant setting, HER2 positive tumors tend to have shorter DFS/OS when treated with tamoxifen. Recent trials using Herceptin as a form of molecular targeted therapy in HER2/neu positive patients have shown promising results in the metastatic setting.¹⁷ Its role in the adjuvant setting is as yet unsettled.

TUMOR SUPPRESSOR GENES

P53 suppressor gene, located at Chromosome 17p13, is a

common gene which is mutated in breast cancer.¹⁸ The loss of suppression of growth factors lead to uncontrolled proliferation of the tumors. Though theoretically it should have direct impact on OS/DFS, there is no strong evidence to suggest that p53 alone can be used in clinical decision making. There is strong association with DNA ploidy and the measures of proliferation, steroid receptors and nuclear grade.

Nm23 is a tumor suppressor gene responsible for regulating metastasis. However, clinical trials could not demonstrate any effective advantage over standard biomarkers.

MEASURES OF INVASIVENESS

a. Cathepsin D is a glycoprotein which is a protease-type enzyme responsible for degrading the basement membrane and thus facilitating invasion.¹⁹ Most trial reports are conflicting. A recent study shows that tumors with higher cathepsin D concentration in the stroma are associated with poorer outcome.

b. Plasminogen activator inhibitor - urokinase-type plasminogen activator (uPA) is an enzyme which binds to a receptor (uPAR). This converts plasminogen to plasmin which in turn activates type IV collagenase. This degrades the collagen of the basement membrane and increases the invasive potential of a tumor. uPA activity is regulated by two natural inhibitors, viz plasminogen activator inhibitor 1 (PAI-1) and plasminogen activator inhibitor 2 (PAI-2). Present review of literature suggests that raised uPA and PAI-1 is associated with worse outcome²⁰. Thus, it appears that PAI-1 does not act as inhibitor. On the contrary, high

PAI-2 levels were associated with longer survival. At the present moment there is good promise in favor of this system and it may actually be important for development of newer molecules.

c. Laminin receptor: the role is unclear presently.

ANGIOGENESIS

From the onset, the growth of a tumor depends on neovascularisation or angiogenesis. This led to the idea of counting microvessel formation in a tumor and to search whether it has any prognostic significance.²¹ There is good evidence to suggest that it is a strong independent predictor of DFS in node negative patients (RR of relapse is 5.78 after 62 months) as also of OS (RR of 3.27). The evidence is very impressive but most of the trials included small numbers of patients and need longer follow-up to determine clinical outcome.

CONCLUSION

It is obvious that the utility of the newer prognostic markers in a biologically and clinically heterogeneous disease like breast cancer can only be determined in carefully designed, large, prospective trials using multivariate analysis. Most of the studies do not meet the required criteria to establish the validity in clinical practice. The unequivocal factor which acts as the pivot of prognosis is the axillary nodal status.

However, as things stand today, node-negative patients can be risk-stratified using age (>35 years), histological subtype and grade (2cm), and ER status (ER+ good, ER- poor). Depending on this, in the low-risk group (