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EDITORIAL

Is there any role for new prognostic markers in breast cancer?

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Breast cancer is heterogeneous in its development, progress and response to treatment. In the initial stages, surgery is usually the first treatment option; however, the risk of recurrence and death has been associated with certain clinical and biological variables, including nodal involvement, histological grade, degree of endocrine responsiveness, HER-2 amplification and tumour size [1]. For over ten years, recognition of the intrinsic subtypes of breast cancer has allowed the disease to be classified into different types, with the use of adjuvant therapies tailored to the biological profile of each type [2–4]. Different genomic platforms have been developed to help clinicians and patients make the best decision regarding adjuvant therapy. The Oncotype DX platform estimated the risk of recurrence in tumours with hormone sensitivity criteria, and defines more precisely which patients will not benefit from receiving a particular chemotherapy regimen and those that will. The TransGEICAM study in 107 hormone receptor-positive and lymph node-negative patients detected a change in the type of treatment in 32% of cases: 21% from chemohormone therapy to hormone therapy and only 11% from endocrine therapy to the combined chemotherapy and hormone therapy. High histological grade and elevated Ki67 were associated with increased recommendation for chemotherapy, whereas progesterone receptor expression was associated with a recommendation for hormone therapy alone [5]. Other genomic signatures provide a dichotomous outcome of good or poor prognosis and, on this basis, indicate a recommendation to not administer chemotherapy in the first case while this treatment should be given in the second. However, validation of these platforms was made on the basis of retrospective randomised studies using treatment regimens which are scarcely used today.

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Moreover, some researchers have shown that the clinical criteria supporting the decision to give a complementary treatment do not always match the information obtained from DNA expression arrays; for this reason two large multicentre studies, MINDACT and TAILORx, were designed in which patients have been randomised to receive endocrine therapy or a combination according to clinical or genomic tumour characteristics. The results of these trials are pending.

Additionally, the use of genomic signatures has other limitations. Firstly, they provide a static view of the disease and cannot estimate the hypothetical volume of residual disease. Moreover, they do not indicate the best drug for each tumour. Finally, the high cost of these studies renders it difficult to incorporate them into daily practice.

In recent years, considerable efforts have been made to gain insight into the biology of tumours, both in their genesis and progression. Signal transducer and activator of transcription (STAT) proteins transmit signals produced by the activation of the transmembrane receptors, which activate some genes involved in cell proliferation, angiogenesis and cell migration [6]. There are seven STAT genes in mammals derived from the ancestral Stat93E gene. STAT proteins are activated by tyrosine phosphorylation following recruitment to ligand-activated receptor complexes. This phosphorylation allows STAT dimerisation and accumulation within the nucleus. STAT3 is activated by phosphorylation of Tyr705 by c-Jun NH2-terminal kinases, growth factor tyrosine kinases or other mechanisms. STAT3 dimers move to the nucleus, bind to specific DNA target gene transcription promoters, and stimulate proliferation and prevent apoptosis in different types of tumour cells [6, 7].

STAT3 has been proposed as a prognostic factor in node-negative breast cancer patients and STAT5 plays a role in predicting response to endocrine therapy [7, 8]. In a retrospective study of 346 node-negative tumours, nuclear expression of STAT3 was observed in 23.1% of cases and Phospho-STAT3 (Tyr705) in 43.5%; both were associated with a lower risk of recurrence and longer survival. Multivariate analysis showed phosphorylation of STAT3 to be an independent prognostic factor for survival in this group, with no relation to hormone receptor expression, proliferation index or HER-2 amplification [9].

The study presented by Sonnenblick et al. [10] analysed 310 breast cancer patients, 125 of whom had lymph node involvement. Nuclear expression of Phospho-STAT3 was observed in 28% of cases and this expression was associated with a lower risk of recurrence and death, being an independent prognostic variable, with no correlation with hormone receptor expression or the degree of cytoplasmic differentiation. However, in patients without lymph node involvement no influence on disease-free interval or survival was found. Apparently, in this series, less than 10% of tumours had HER-2 amplification, and perhaps for this reason, did not show any interaction between these two variables.

Although these results point to the nuclear expression of Phospho STAT3 as a predictor of better prognosis, a recent study with 141 node-negative breast cancer patients observed that STAT3 pathway activation was associated with an increased risk of recurrence and distant metastasis [11]. The heterogeneity of tumours is recognised in different studies. Marotta et al. proposed the existence of two cell populations: one with stem cell characteristics of (CD44+ CD24–) and the other with a further differentiation profile (CD44– CD24+). They identified a group of 15 genes that regulate the proliferation of the first group of cells and the inhibition of many of these genes, including IL-6, PTGIS, CXCL3, PFKFB3 and HAS-1, which influence STAT3 activation. STAT3 phosphorylation is determined by the activation of JAK2, which depends on the function of IL-6. The IL-6/JAK2/STAT3 pathway plays an important role in the proliferation of more undifferentiated cells and in the ability of a tumour to divide and spread [11].

Despite deeper biological knowledge of breast cancer, the identification of a new marker to estimate the prognosis of the disease is of interest; however it will not facilitate a better selection of specific drugs for treatment in a given patient. This would need several prospective studies that stratify patients according to the level of expression of a variable such as Phospho-STAT3. However, recognition that other signalling pathways may be activated or inhibited in the same tumour may help to better define the strategies of additional systemic therapy. To date, we have relied on clinical and histological variables, but the results awaited of prospective randomised trials based on the result of gene expression platforms will be useful for patients. However, the incorporation of new variables as prognostic markers of breast cancer would not make sense if they did not enhance precision in treatment selection.

Most of the published series did not describe the type of systemic adjuvant therapy administered to patients or the selection criteria employed. Sonnenblick et al. reported that 86% of the patients received chemotherapy, with more than half the cases receiving anthracyclines [10]. Adjuvant systemic therapy reduces the risk of recurrence and the magnitude of this reduction varies according to the chemotherapy regimen used. Different randomised clinical trials have demonstrated the effectiveness of taxanes in adjuvant treatment, especially in node-positive breast cancer patients. It will be interesting to address the possible influence of a proposed new prognostic marker in this setting.

Challenges for the future will be to demonstrate the usefulness of certain biomarkers in identifying women at risk for recurrence and who may benefit from a specific adjuvant therapy; at the same time, establish the best systemic therapy strategy adapted to the expression of genes related to proliferation and cell spread; and last but not least, to dynamically verify the effect of the therapy administered.

References

1. Goldrirsch A, Ingle JN, Gelber RD et al (2009) Thresholds for therapies: highlights of the St Gallen International Expert Consensus of the primary therapy of early breast cancer 2009. Ann Oncol 20:1319–1329
2. Perou CM, Sorlie T, Elsen MB et al (2000) Molecular portraits of human breast tumours. Nature 406:747–752
3. Prat A, Perou CM (2011) Deconstructing the molecular portraits of breast cancer. Molec Oncol 5:5–23
4. Goldrirsch A, Wood WC, Coates AS; panel members (2011) Strategies for subtypes–dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2011. Ann Oncol 22:1736–1747
5. Albanell J, Gonzalez A, Ruiz Borrego M et al (2011) Prospective transGEICAM study of the impact of the 21-Gene Recurrence Score assay and traditional clinicopathological factors on adjuvant clinical decision-making in women with estrogen receptor-positive (ER+) node-negative breast cancer. Ann Oncol [Epub ahead of print] doi: 10.1093/annonc/mdr278
6. Aaronson DS, Horvath CM (2002) A road map of those who don't know JAK-STAT. Science 296:1653–1655
7. Tweardy D, Chang JC (2011) Stat5: from breast development to cancer prognosis, prediction and progression. J Clin Oncol 29:2443–2444
8. Yamasmita H, Nishio M, Ando Y et al (2006) Stat5 expression predicts response to endocrine therapy and improves survival in estrogen receptor-positive breast cancer. Endocr Relat Cancer 13:885–893
9. Dolled-Filhart M, Camp RL, Kowalski DP et al (2003) Tissue microarray analysis of signal transducer and activators of transcription 3 (Stat3) and phospho-Stat3 (Tyr705) in node-negative breast cancer shows nuclear location is associated with a better prognosis. Clin Cancer Res 9:594–600
10. Sonnenblick A, Shriki A, Galun E et al (2012) Tissue microarray-based study of patients with lymph node-positive breast cancer shows tyrosine phosphorylation of signal transducer and activator of transcription 3 (tyrosine705-STAT3) is a marker of good prognosis. Clin Transl Oncol 14:232–236
11. Marotta LC, Almendro V, Marusyk A et al (2011) The JAK2/STAT3 signalling pathway is required for growth of CD44+CD24– stem cell-like breast cancer cells in human tumors. J Clin Investig 121:2723–2735