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Review

Prognostic factors of early breast cancer☆

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ABSTRACT

Decision about the administration of adjuvant therapy for early breast cancer depends on the evaluation of prognostic factors. Lymph node status, tumour size and grade of differentiation are classical variables in this regard, and can be complemented by hormonal receptor status and HER2 expression. These factors can be combined into prognostic indexes to better estimate the risk of relapse or death. Other factors are less important.

Gene profiles have emerged in recent years to identify low-risk patients who can forgo adjuvant chemotherapy. A number of profiles are available and can be used in selected cases. In the future, gene profiling will be used to select patients for treatment with new targeted therapies.

Factores pronósticos en el cáncer de mama en estadio inicial

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RESUMEN

La decisión de administrar un tratamiento adyuvante del cáncer de mama en estadio inicial se fundamenta en la evaluación de varios factores pronósticos. El estado de los ganglios axilares, el tamaño del tumour y el grado de diferenciación histológico son las variables consideradas como clásicas, que se ven complementadas con el estado de los receptores hormonales y la expresión de HER2. Estos factores pueden combinarse con índices pronósticos para tener una estimación más precisa sobre el riesgo de recaída o de muerte asociada a la neoplasia. Otros parámetros individuales tienen una importancia secundaria.

En los últimos años, a los factores clásicos se les han añadido los perfiles de expresión de genes, que permiten definir qué pacientes pueden prescindir de la quimioterapia adyuvante cuando el riesgo de recaída estimado es bajo. Se encuentran comercializados diferentes perfiles y se emplean de forma rutinaria en casos seleccionados. En el futuro, los perfiles génicos servirán para seleccionar grupos de pacientes que se beneficien de nuevos tratamientos dirigidos.

Introduction

Breast cancer is one of the most common types of tumours and provokes the greatest amounts of the cancer-related deaths in our environment.[1] The future of patients diagnosed with this type of cancer has progressively improved for 2 basic reasons: early diagnosis, which ensures identification of the tumour when it is still small, and the use of adjuvant treatments, which reduce the risk of relapse.[2] Adjuvant treatments include radiation, chemotherapy, anti-HER2 and hormone therapies. Depending on each individual patient, choosing one or more of these options to increase efficiency and minimise the possibility of an eventual relapse is necessary.

The criteria for selecting one or another type of complementary treatment are well established. For example, radiation therapy is recommended after conservative breast surgery or when lymph nodes under the arm have been affected.[3] Hormonal therapy should be recommended when the tumour expresses oestrogen or progesterone receptors,[4] whereas the monoclonal antibody anti-HER2 trastuzumab is administered in cases of over-expression of the

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HER2 protein.[5] The case for chemotherapy is different because there is no predictive response marker. Consequently, the benefits involved are not always of the same magnitude, and in certain circumstances this type of therapy does not provide the patient with any real benefits, it only entails risks of side effects.

Analysing the prognosis of the disease is essential in estimating the benefit of adjuvant chemotherapy. In general, the higher the risk of relapse, the greater the margin of positive results. Extensive research into detecting the variables associated with a better or worse prognosis has been being carried out for many years. The literature on the subject is abundant, while at the same time somewhat unfocused. The purpose of this review is to focus on the most important factors affecting clinical practice in this area.

Clinical factors

Age: patients who are under 35 years-old have a worse prognosis than those who are older.[6] The tumours they suffer are usually high-grade, have no expression of hormone receptors and have lymphovascular invasion. They are all unfavourable factors, as discussed below. There has been talk of other clinical parameters related to prognosis, such as an advanced age, race or economic status, but they have no real independent value.

Anatomopathological factors

The presence of metastases in the axillary lymph nodes is the most important prognostic factor in breast cancer. When there is no lymph node invasion, the probability of survival is around 90% at 10 years after surgery, whereas when an invasion does exist, the risk of death multiplies by a factor of 4–8. The relationship is linear: the greater the number of nodes involved, the lower the survival rate. Cases that have been monitored showed that, after 10 years, there is a less than 20% survival rate when there are 4 or more lymph infiltrators.[7] Although in recent years these results have improved due to the use of improved chemotherapy treatments and adjuvants radiotherapy,[8–10] axillary involvement remains the main adverse parameter in localised breast cancer.

Currently, there are few patients who start with bulky lymph node involvement. This has meant that the selective sentinel node biopsy has become the standard surgical procedure on the armpit. Several prospective studies have shown that the sentinel node is affected by the tumour in 20% of cases.[11] Survival rate is approximately 90% if this is the only node invaded by the tumour, and can even exceed 95% for the relatively frequent case where involvement is in the form of micrometastases of sizes between 0.2 and 2 mm. When micrometastases are detected in the sentinel node, a lymphadenectomy is usually not carried out since the probability that more lymph nodes are involved is low and the prognosis is better compared to cases with macroscopic involvement.[11–13]

The size of the primary tumour is the second most important parameter and also has a linear relationship with the prognosis. Survival is at 90% in tumours less than 1 cm and 70% in tumours ranging between 2 and 5 cm.[14]

Recently, there has been talk of other factors, such as: the presence of tumour cells in the bone marrow or peripheral blood and tumour infiltration by T lymphocytes. Two large studies found evidence of tumour cells in the bone marrow in 15–30% of patients with localised breast cancer; its presence increased the risk of death by between 2 and 4 times.[15,16] More recently, the detection of tumour cells in peripheral blood has been considered a less aggressive alternative to bone marrow biopsy to detect the tumour outside its primary bed. Both factors maintain their prognostic value in the multivariate analysis.[17] However, the technical difficulty of carrying out the assessments – in addition to the disturbance of the bone marrow biopsy – has prevented the use of these factors becoming widespread.

Infiltration of cytotoxic T lymphocytes into the tumour bed has been acknowledged as a favourable parameter. One study found a 28% decrease in the risk of death when these lymphocytes were detected in triple-negative tumours (negative for oestrogen, progesterone and HER2 receptors) or in positive ones for HER2.[18] Other studies that focused on triple-negative tumours found that the prognosis improved as the degree of infiltration by these lymphocytes increased.[19] It is unclear why the relationship exists: it may indicate some degree of activity by the patient's immune system against the tumour or an increased sensitivity to chemotherapy.

The usual histological varieties of breast cancer are ductal carcinoma (80%) and lobular (15%). There are rare varieties, the following of which have good prognosis: tubular, adenoid cystic, medullary, apocrine and cribiforme. By contrast, the following have a poor prognosis: pleomorphic, metaplastic and high-grade neuroendocrine.[20]

Factors related to tumour biology

The tumour differentiation grade is an independent parameter of the size and axillary lymph node status. It is generally determined with the Bloom–Richardson system. It has the problem of the dependent observer variability, but the results reported show certain consistency. A large study from the *Surveillance, Epidemiology*, and *End Results Programme* in the US indicates that the histological grade provides additional information for each possible combination of size and lymph nodes.[21] For example, in tumours of less than 2 cm and no lymph node, the 10-year survival is 97% for grade 1 and 89% for grade 3, grade 2 falling in between those two percentages.

The differentiation grade must be distinguished from the expression of the Ki-67 protein, a marker of cell proliferation. This variable has been criticised because of its variability when assessing between different observers. Several studies conducted a centralised assessment and found that tumours with positive hormone receptors and Ki-67 $\geq$ 14% expression had a higher risk of relapse,[22,23] but other studies have failed to show this association.[24]

Lymphovascular invasion, plasminogen activating factor expression or p53 expression has little predictive value. When analysed individually, they distinguish populations with different survival rates, but provide little additional information when combined with more significant parameters (such as lymph node involvement, the size and differentiation grade). There are many other genes that have shown some sort of prognostic value in isolated studies, but they are in the same situation and are not used. Tumours expressing oestrogen and progesterone receptors have a better prognosis than those with negative receptors.[25] However, the main value of determining hormone receptors is not for reasons of prognosis, but for predictive reasons, as it facilitates recommending a specific treatment such as hormone therapy.

HER2 is a prognostic and predictive response parameter. Tumours with an over-expression of this protein have a more aggressive course[26] and can be treated with specific medications such as trastuzumab. The prognosis of this disease has improved substantially since trastuzumab began to be used with the standard adjuvant treatment.[10,27]

Tumours that do not express hormone receptors or HER2 are called "triple-negative". They tend to be poorly differentiated tumours and have high growth rate, in addition they lack the possibility of adjuvant therapy with hormones or trastuzumab. Recently the possible value of the androgen receptor in small-size triple-negative tumours has been suggested.[28]