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Breast cancer biomarkers: Prognosis and prediction

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INTRODUCTION

Despite the great advances in prevention, screening, early detection and better treatment, most of the advanced breast cancer (BC) patients will eventually die because of their disease. Nearly half of all operable BC patients, having been diagnosed with the disease localized to the breast and regional lymph nodes only, will develop the metastatic disease, despite the radical surgery followed or not by radiotherapy. A substantial part of these women can be cured only by surgery. In those patients, who will develop the recurrent disease due to the coexisting micrometastases at diagnosis, the adjuvant treatment may improve the outcome, either by delaying the local or distant recurrence and death, or by the preventing of disease spreading. This means, the adjuvant treatment prolongs the disease-free (DFS) and overall survival (OS), or even cures some patients.

PROGNOSIS

The risk of disease recurrence can be estimated by using the combination of prognostic factors, which indicate the probability of the micrometastases existence in an individual patient, or in a group of patients. However, the contribution of different prognostic factors to the risk level must be neither of the same quality, nor of the same quantity. For example, the high number of involved lymph nodes strongly suggests that the larger proportion of patients develop the disease relapse, but it does not tell us anything about the relapse localization, its aggressiveness, endocrine or chemotherapy responsiveness etc. On the contrary, the estrogen receptor (ER), as a prognostic marker, indicates less strongly the proportion of relapsing patients and the localization of the first relapse. Nevertheless it is the most powerful marker of tumor behavior and predictor of the response to endocrine therapy (1). According to the risk for recurrence, patients can be divided into subgroups with better and poorer prognosis, but we can predict neither the disease relapse, nor the time of the relapse occurrence in an individual patient. Therefore, 'prognosis' means the probability not only of having micrometastases, but also includes the probability of having the favorable or unfavorable site of micrometastases, or having the slow or fast growing tumor.

It was found that the chronobiological age, tumor size and lymph node involvement determine the prognosis, as the most powerful factors. Tumor grade, markers of proliferation and invasion seem to be good markers of biological aggressiveness and tumor behavior. Age is thought to have the specific discontinuous prognostic influence: it was found that women, younger than 35 years, have significantly poorer prognosis than older women, irrespective of other prognostic variables (2). These factors, named classical, are well established. All other new prognosticators should be investigated in relation to their prognostic value.

Again, steroid receptors are less powerful prognostic factors. This means that SR+ patients, untreated with any adjuvant therapy, will live slightly longer, and will relapse less frequently, compared to the corresponding SR negative patients. However, SR status alone cannot be used, by itself, for the decision whether the patient should, or should not be treated at all.

The value of one prognostic factor should be investigated in patients not treated by any adjuvant therapy, because the systemic and adjuvant treatment is used with the aim to change, i.e. to improve the outcome. The investigation of prognostic role of new potential prognostic factors may be done in several patients' groups, first of all, in the groups that did not receive any adjuvant therapy for the passed several years, according to the previous consensus. The tissue samples, taken at diagnosis, can be used for testing the new markers. However, even if patients were included in a randomized study, the aims of those studies, the kind of sample taken and stored, as well as other conditions - put such marker studies in a type III Level Of Evidence (LOE III). Second group consists of patients, who are currently diagnosed, and belong to a group, which does not need to be treated, according to the current guidelines. Those studies will be prospective, and allow the proper sampling of tissue or serum; however, they will last long, due to the small number of appropriate patients. The third group of patients consists of those, who have finished the standard adjuvant treatment, according to the current consensus and then the tissue or serum samples are taken to determine the marker prognostic value. The example of such studies is the tissue or serum sampling after the neoadjuvant/adjuvant chemotherapy and surgery (3).

In clinical practice, prognostic factors can help in the decision which women should be treated with adjuvant treatments.

BIOMARKERS AS PREDICTIVE FACTORS

The prediction is the probability of the therapeutic response to a particular adjuvant treatment. Thus, the predictive factors are those tumor characteristics that can help us in a decision which adjuvant treatments should be used in a particular patient.

Currently, steroid receptors are the only predictive factors, recommended for routine clinical practice. It is well known how strong is the predictive value of SR for the response to tamoxifen, and other endocrine therapies, in SR+ patients. In adjuvant settings, tamoxifen reduces the death risk from BC for as much as 50%, in postmenopausal ER+ BC patients (4).

Although the current guidelines for adjuvant treatment offer the optimal treatment to all patients, many of them will eventually develop the recurrent disease and die from breast cancer. This was the reason why so many biological markers are investigated, as prognostic and predictive determinants. The main goal is to improve the use of adjuvant therapy and the outcome. Some of those markers almost reach the critical amount of evidence to be included in standard protocols, while others are far from the recommendation for their clinical use. Several of most promising biomarkers will be discussed elsewhere, in this issue. However, some of the controversial aspects of well-established prognostic and predictive markers will be pointed out.

BIOMARKERS THAT IMPROVE THE PREDICTIVE VALUE OF ER

Progesterone receptor (PR) is one of the first biomarkers included in clinical practice, as the estrogen-regulated protein that improved the prediction of endocrine responsiveness. It is well known that the overall response rate of metastatic breast cancer could be predicted in a significantly larger proportion.
of patients by the use of both SRs (5). There are several other biomarkers, being currently investigated for their ability to improve the prediction of endocrine responsiveness (Cathespin D, bcl-2, pS2). However, their clinical usefulness is still controversial (6, 7). Biomarkers that predict the endocrine unresponsiveness in BC patients are equally interesting - the epidermal growth factor receptor family is being currently the most investigated (the overexpression of c-erbB-2/neu or HER-2 and EGF-R). However, their clinical usefulness, especially in SR+ early BC patients is still controversial (8). Moreover, it seems that the predictive value of HER-2 need not be the same, for the response to tamoxifen and aromatase inhibitors (9).

**SRS IN THE PREDICTION OF RESPONSE TO CHEMOTHERAPY**

For many years, it has been widely accepted that the response to adjuvant chemotherapy does not depend on the SR status. In other words, the patients with SR+ and SR-negative tumors would have the equal chance to respond. An exceptional opposite opinion (10) was neglected. The meta-analysis recently reported, renewed the interests for this concept, since it was found that the women whose tumors were ER-negative, could have a greater benefit from chemotherapy, than those with ER+ tumors (11). Similar conclusion was suggested in the intergroup clinical study of AC chemotherapy with or without paclitaxel (12).

**OTHER PREDICTORS OF THE RESPONSE TO CHEMOTHERAPY**

However, other biomarkers that predict the response to chemotherapy are currently being the most extensively investigated. The different predictive role of HER-2 in relation to the response to CMF chemotherapy, anthracycline-based chemotherapy, and possibly taxanes, although still controversial, is expected to be elucidated in the several clinical studies (13).

In spite of several methodological problems, there is evidence from clinical studies that p53 could be the promising predictive biomarker in breast cancer. While the specific mutation of p53 is related to anthracycline resistance (14), the response to taxanes was independent on p53 status (15). Further investigation of this concept could influence the current algorithm of systemic and adjuvant chemotherapy regimens.

**CIRCULATING BIOMARKERS**

Respectable number of investigations are nowadays focused on circulating tumor-associated biomarkers, due to its easy monitoring and avoidance of surgical tumor sampling. Serum levels of ectodermal domain of HER-2 (16), plasma transforming growth factor-β1 (17), plasma DNA found outside of primary tumor, plasma IGFs, are some of the currently investigated biomarkers, either as prognostic, or predictive factors in the breast cancer management.

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