EDITORIAL

BREAST CANCER MOLECULAR PROFILE. A NEW CHALLENGE IN CLINICAL ONCOLOGY

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Breast cancer is the most frequent malignancy in female, and in 2015, only in U.S. there were estimates over 230.000 new cases and over 40.000 specific deaths (1). Although the incidence of breast cancer did not increase dramatically in last years, both morbidity and mortality remain high, despite real progresses made in the fields of early diagnosis and treatment. The outcome of patients with breast cancer was improved in last decades by early detection, development of a more effective chemotherapy, long-term effects of hormone-therapy, and introduction of targeted therapy (2). Development of new biomarkers and standard procedures for the molecular characterization of breast cancer is helpful not only in the diagnosis, but also in predicting the response to therapy. Despite extensive researches on the clinical and molecular characteristics of breast cancer, the personalized therapy is still a challenge.

Almost three decades ago there were introduced in clinical practice the first markers with direct impact on adjuvant therapy. Hormone receptors, the epidermal growth factor receptor-2 (HER2) and Ki67, which shows the proliferation rate, opened the era of targeted therapy in patients with breast cancer. Currently, four markers are performed in virtually every laboratory that processes breast cancer biopsies (estrogen receptors, progesterone receptor, HER2, and Ki67). Based on the combined expression of these markers, soon was born the concept of triple negative tumors, and recognized as aggressive and less responsive to therapy. The immunohistochemical expression of hormone receptors and HER2 protein in tumor cells is an indication for specific adjuvant therapy with anti-estrogen receptor inhibitors or trastuzumab. On the other hand, not all the cases that show hormone receptors expression do respond to hormone therapy and resistance to trastuzumab therapy has been already documented. Along the last ten years various mechanisms were proposed to explain resistance to therapy, but a real explanation and its impact on clinical significance is still lacking.

Breast cancer is a heterogeneous disease and the conventional pathologic classification stratifies the cases based only on morphologic criteria. For more than hundred years conventional pathology was thought to be the 'golden standard' in the diagnosis of breast cancer. Although essential in diagnosis, grading and prognosis, the pathologic report brings only few useful information on adjuvant therapeutic strategy, and even more, it brings no information on the potential response to targeted therapy. Virtually, molecularly distinct subtypes were conventionally grouped based on pure morphologic features. Therefore, it was clear the necessity to develop a new approach of breast cancer, which can be helpful to personalized therapy.

A very important moment in the understanding of breast cancer biology was marked by the gene analysis and characterization of five major types, based on the expression of estrogen (ER), and progesterone receptors (PR), HER2, cytokeratin 5/6 (CK5/6), epidermal growth factor receptor (EGFR), and p53 (3, 4). Types that were originally defined were Luminal A, Luminal B, HER2, basal-like and normal-like or unclassified. Gene analysis cannot be performed in all the cases because the huge number of patients. Many authors have shown that immunohistochemistry is a very good surrogate of gene analysis and applying a panel of five antibodies can give reliable information on the molecular type of breast cancer (5). Later, Ki67 was found useful to discriminate between luminal types and added to the panel. Other surrogate markers as Bcl-2, E-cadherin or Cytokeratin 18 were also investigated, but their role in the stratification of patients remains under debate.

The molecular classification had an immediate impact on the therapeutic strategy, and even more, it contributed to a better understanding of long term prognosis. At present time, it does not give significant information about the potential response of tumor cells to specific therapy, but some procedures are addressed to restricted subgroups of patients.

Currently, almost all laboratories evaluate the molecular profile of the primary tumor. There are very few information about the molecular profile of lymph node and distant metastases. In the last years, there were reported significant discordances in the molecular profile of the primary breast cancer and synchronous lymph node metastasis (6, 7, 8, 9). These findings significantly change our perspective on the progression of breast cancer, and it has a major impact on the therapeutic strategy (10, 11). We have shown that in 19.7% of the cases there is a significant difference in the molecular profile between the primary tumor and corresponding lymph node metastases (12). We have found that the

most common switch is from Luminal A to Luminal B, and the most stable subtype is HER2. In addition, we have demonstrated a differential expression of E-cadherin in the primary versus synchronous lymph node metastases (13). Similar data were reported in patients with distant metastases (14, 15). The divergent molecular profile of the primary tumor and the corresponding lymph node metastases may explain (maybe only in part) the overtreatment in some cases and under treatment in others (16). Could be a relationship between this aspect and resistance to a given adjuvant or/and targeted therapy? Until now, it is difficult to answer this question, and further studies on large series are necessary. What we have to keep in our mind is the unstable character of molecular markers expressed by tumor cells along progression and development of lymph node and distant metastases.

Based on these data, it seems that evaluation of basic molecular markers is mandatory in both primary tumors and axillary lymph nodes, and therapy should be adapted accordingly. This is why in Research and Clinical Medicine are accepted and published many articles about the molecular profile of breast cancer and its impact on angiogenesis, tumor stroma, and tumor cells themselves. They all contribute to a better understanding of the natural evolution of breast cancer, and hopefully, will identify, characterize, and use new targets for therapy.

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