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Personalized medicine: Present and future of breast cancer management

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Abstract

Breast cancer is the first cause of cancer in women worldwide. Recent molecular analyses have shown that it is not a single disease but a mixture of several diseases with different biological behaviors, which should lead to treatment customization for each patient. Personalized medicine is based on tumor and/or patient molecular profiles. This new way to think oncology is currently applied at different stages of breast cancer management, including prognosis, prediction of treatment efficacy, and development of new therapies *via* new kinds of clinical trials. These trials are not only based on tumor site but also on tumor genetic characterization using genomic tools such as gene expression profiling, array-CGH or next-generation sequencing technologies. The aim of personalized medicine is to tailor treatment according to the specificities of a single disease in a given patient. In this review, we present the advances in treatment personalization which are currently used in daily practice as well as the technologies and therapies under investigation in various clinical trials.

Keywords: Breast cancer; Personalized medicine; Molecular profiling

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1. Introduction

Breast cancer (BC) is the first cause of death by cancer in women worldwide, with nearly 465,000 deaths in 2011 [1]. BC is a heterogeneous disease with several clinical, pathological and prognostic subgroups. Such diversity is the result of a large range of molecular alterations. Since a decade, high-throughput technologies have allowed to better understand this molecular complexity, poorly reflected by usual histo-clinical features and scarcely exploited by former therapeutic approaches.

Personalized medicine has been defined by the National Health Institute and the Food and Drug Administration (FDA) as "an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease" (accessed January 3rd, 2013) and as the best way to obtain "the best medical outcomes by choosing treatments that work well in a given person according to its genomic profile, or with certain characteristics in blood or cell surface proteins" [2]. The first goal of this new way to think oncology is to define new subgroups of patients more homogeneous in terms of therapeutic response and outcome. Molecular classifications should allow clinicians to improve the treatment of each class. These biomarkers must be specific, measurable, reliable, and linked to specific biological processes [3]. They can be identified at molecular (DNA, RNA, proteins) or cellular levels, using biological fluids (blood, serum, plasma, urines), tissues, or morphological and functional radiological assessments. They should improve diagnosis, prognostic evaluation, treatment or follow-up when compared to usual features [4].

This review will present the main biomarkers, currently available and under development, in BC. The development of a more tailored medicine will be based on prognostic biomarkers guiding the indication or not of systemic therapy, and predictive biomarkers guiding the choice of a given systemic therapy, in both adjuvant and metastatic settings.

2. Prognostic and predictive biomarkers in early breast cancers

2.1. Molecular subtypes

For many years, breast cancer has been considered as a single disease displaying variable clinical, morphological and biological features. Some of these features have a prognostic and/or predictive value useful for guiding the indications for adjuvant systemic treatment (chemotherapy (CT), hormone therapy (HT), HER2 inhibitors): patient's age, pathological tumor size, axillary lymph node involvement, grade, vascular emboli, expression of hormone receptors (HR, including estrogen receptor (ER) and progesterone receptor (PR)) defined using immunohistochemistry (IHC), and expression of HER2 (IHC) and/or *ERBB2* amplification (*in situ* hybridization technologies). Because IHC has a few limitations (reproducibility, standardization and quality controls), alternative ways to define HR and HER2 status are being explored. They include quantitative measurement of mRNA expression based on DNA microarrays or quantitative RT-PCR [5–7], and multigene expression signatures of pathway activity, theoretically more reliable than single protein or gene expression [8]. Among the numerous other tested biomarkers, the uPA (urokinase-type plasminogen activator) protease and its inhibitor PAI-1 (plasminogen activator inhibitor-1), both markers of invasion, have reached the highest level of evidence with the validation of their value both prognostic and predictive for benefit of adjuvant CT in a prospective randomized trial [9]. In node-negative patients, low uPA/PAI1 protein expression levels were associated with better outcome, whereas the benefit of adjuvant CT was higher in patients with high uPA/PAI1 levels [9]. Today, uPA/PAI1 assessment is considered by ASCO as a level 1 biomarker for node-negative early BC [10], but is very rarely used for practical reasons (ELISA test from 50 mg of cytosol protein sample extracted from frozen tumor sample).

More than 10 years ago, gene expression profiling based on DNA microarrays [11] revealed the molecular heterogeneity of BC [11]. A new molecular classification was defined, dividing BC in at least 5 biologically and clinically relevant subtypes [12,13]: luminal A (LA), luminal B (LB), basal-like (BL), HER2-enriched and normal-like (NL). These subtypes are linked to major molecular alterations such as HR and HER2 expression and proliferation and to mammary cell types. They are found across all BC stages, from *in situ* carcinoma [14] to inflammatory [15] and metastatic tumors [16], and display epidemiological specificities, different rates of therapeutic response and different outcomes. LA tumors are less proliferative, poorly chemosensitive but highly sensitive to HT. In the opposite LB, HER2-enriched and BL cases are generally resistant to HT but sensitive to CT [17]. Since these subtypes incorporate many of the prognostic and predictive features used in previous recommendations, the 2011 Saint-Gallen Consensus Conference based its recommendations on the molecular subtypes [18]. For practical reasons, the subtypes were approximated using four IHC markers (ER, PR, HER2, Ki67) [19] rather than gene expression profiles [20], even if a genomic test – the *Breast BioClassifier/PAM50* (50 genes, Nanostring Technologies®, USA) – has been recently commercialized and can be applied to paraffin-embedded BC samples. Systemic therapy recommendations followed the subtype classification: LA tumors require only endocrine therapy that is also given to patients with LB tumors. Chemotherapy is indicated for most patients with LB tumors, HER2+ tumors also treated with trastuzumab, and triple-negative ductal tumors. These recommendations have been essentially unchanged during the 2013 Saint-Gallen conference [21] for HER2+ tumors and triple-negative ductal tumors. But because the main clinical issue concerns the selection of patients with HR+/HER2− tumor (node-negative or with less than four positive nodes) candidate for adjuvant