ABSTRACT

Progress in sequencing technology made it possible to analyze breast tumors in great details and identify numerous genomic alterations with essential role in precision medicine. Comprehensive genomic profiling confirmed not only the role of already known breast cancer genetic alterations like BRCA1/2, TP53, PIK3CA, ERBB2, PTEN mutations, but also led to the identification of new mutations relevant for personalized treatment of breast cancer. Several challenges still need to be addressed, but the advances of genomic-driven precision medicine in breast cancer is having a huge impact on those women afflicted by this disease.

KEY WORDS

Breast cancer; genomic profiling; precision medicine; treatment

The article provides the insights of current status of breast cancer precision medicine.

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Breast cancer is one of the most common female malignancies, affecting one in eight women. In the U.S., there were about 232,000 newly diagnosed breast cancer cases and about 40,000 deaths from breast cancer in 2015 (SEER, 2016) [1]. Since the discovery of BRCA1 and BRCA2 mutations in breast cancer, it has been acknowledged how crucial it is to understand the genetic background of an individual in order to determine breast cancer susceptibility, with important role in prevention and early detection. Breast cancer research contributed immensely to precision cancer medicine by moving at a fast rate from diagnosing breast cancers based on their clinic-pathological characteristics to immunohistochemistry of specific targets like estrogen receptor (ER) and HER2, to gene expression analysis of molecular subsets of breast cancers, to sequencing of breast tumors.

Significant progress in sequencing technology over the last decade has made it feasible to analyze the genomic profile of each tumor, leading to the identification of genetic abnormalities of clinical significance [2]. When tumor genomes are analyzed by sequencing, the coverage of the sequencing, the cost and the depth of the coverage should be considered. The amount of the genome to be sequenced, cost and depth need to be addressed when tumor sequencing is performed to maximize the gains of this type of analysis [3]. Large sequencing studies have confirmed the role of well-known breast cancer-related genes like BRCA1/2 genes and have also identified other genes recurrently mutated in breast cancer.[4] Moreover, studying specific breast cancer subtypes like triple-negative breast cancers (TNBC) and BRCA-mutant breast cancers, multiple mutations were revealed in genes not previously linked to breast cancer development [5, 6].

In the recent years, several breast cancer sequencing studies, using whole-genome or whole-exome sequencing, catalogued the numerous genetic alterations observed in different breast cancers molecular subtypes [2, 4-10]. Among the most commonly found mutations were in TP53 (35% of tumors), PIK3CA (34% of tumors), GATA3 (9% of tumors), MAP3K1 (8% of tumors), MLL3 (6% of tumors) and CDH1 (6% of tumors). Breast cancer subtypes presented different mutations profiles. More specifically, TP53 mutations were found in 80% of basal-like breast cancers, 72% of HER2-amplified breast tumors and in only 12% of luminal-A type tumors. GATA3 mutations were present in 14% of luminal-A tumors, 15% of luminal-B tumors and in only 2% of basal-like and HER2-enriched breast cancers [4].

More than 90% of these mutations were point mutations and the rest were small insertions or deletions. Also, copy number alterations (CNAs) like amplifications in HER2, PIK3C, EGFR genes and deletions or loss of PTEN, MLL3, RB1 were observed in different subtypes of breast cancer (Cancer Genome Atlas Network, 2012) [6]. More specifically, luminal A tumors presented fewer CNAs (about 30 rearrangements) relative to basal-like or HER2-enriched breast cancers, showing about 240 rearrangements [8]. Furthermore, it has been reported that the presence of amplified sites such as 8p11–12 (FGFR1), 8q24 (MYC), 11q13 (CCND1), and 17q12 (ERBB2) in high-grade ER+ cancers was associated with poor outcome in multiple studies [9, 10, 11]. Further, a recent study discussed the emerging role of other genomic rearrangements like fusion genes for breast cancer personalized therapy approaches [12].

This improving knowledge of the genomic landscape of breast cancer and better understanding of patient-to-patient variability is advancing our ability to apply the appropriate treatment to the appropriate patient at the appropriate time, a symbol of precision cancer medicine. All these advances led to targeted therapy of an individual genomic alteration with multiple agents like in the case of HER2-amplified breast cancers [13]. For example, HER2-amplified breast cancers have several treatment options including approved monoclonal antibody, Trastuzumab, dimerization inhibiting monoclonal antibody, Pertuzumab, tyrosine kinase inhibitor, Lapatinib. For estrogen receptor mutations, selective estrogen receptor modulators like Tamoxifen and aromatase inhibitors like Letrozole, Anastrozole and Exemestane are used in clinical practice [14]. In addition, specific genomic alterations in other genes may predict sensitivity to the treatment in current use or in clinical development. For PI3-kinase pathway genomic alterations, several PI3K inhibitors, mTOR inhibitors, AKT inhibitors and PI3K/mTOR inhibitors are existing therapeutic options. Several PARP inhibitors are currently used for BRCA1/2 mutations. Similarly, for genomic alterations in fibroblast growth factor (FGFR), insulin-like growth factor (IGF1R) pathways, there are many therapeutic agents that could be used based on individual characteristics of each patient [2, 3].

Furthermore, there are several initiatives in US and Europe to sequence tumor genomes to inform clinical decision making in patients with advanced breast cancer. These initiatives include the “umbrella trials”, which use the genomic profiling of a single type of cancer (e.g. SAFIR and Aiming to Understand the Molecular Aberrations in Metastatic Breast Cancer (AURORA) trials for breast cancer) [15, 16] and the “basket trials” that use multiple tumors profiling to identify common genomic alterations or “actionable mutations” that could be targeted with specific therapies (e.g. NCI’s MATCH (Molecular Analysis for
Therapy Choice) trial [17].

Additionally, it is proposed that three steps should be followed to develop the precision medicine in advanced breast cancers when conducting genomic studies [18]. The first step would include the disease fragmentation process of rare genomic alterations so that drugs are developed for that particular mutation (e.g. AKT1 mutations). Secondly, an alliance of several rare genomic alterations would lead to a molecular profile of the disease, characterized by an altered pathway (e.g. homologous recombination deficiency). The re-unification step would allow the development of bioinformatics algorithms to identify targets in all breast cancer patients (e.g. SAFIRO2 trial) [18].

The advances in technology and bioinformatics in the last 2 decades contributed immensely to the translation of cancer research to clinical practice, changing the lives of those afflicted with breast cancer. There are still challenges ahead but remarkable progress was made in the precision medicine of breast cancer.

CONFLICT OF INTEREST
The author declares no competing interests.

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None.

REFERENCES


