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Review paper

Genetics in breast cancer and treatment strategy : A current scenario

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Abstract

This review aims to sketch the current scenario of breast cancer, which deals with the genetics, treatment strategy, drug resistance and overcomes as well as associated symptoms.

Keywords: *Breast Cancer; Present Circumstances; Medical Science.*

1. Introduction

Breast cancer (BC) is the second-leading cause of cancer death in women. Approximately, 40,000 patients die as a result of it (American Cancer Society 2014). BC develops from breast tissue. Included signs of BC are lumped in the breast, change in breast shape, dimpling of the skin, fluid coming from the nipple, or a red scaly patch of skin. It may associate with bone pain, swollen lymph nodes, shortness of breath, or yellow skin. Along with genetics, obesity, lack of physical exercise, alcohol consumption, hormone-replacement therapy, especially, during menopause, exposure to ionizing radiation, having children late or not at all, older age, and family history are the identified caused of BC. BC most commonly develops in cells from the lining of milk ducts (ductal carcinomas) and the lobules (lobular carcinomas) that supply the ducts with milk. Some BCs develop from pre-invasive lesions such as ductal carcinoma in situ (Christobel and Sunil 2009; Breast Cancer Treatment 2014; World Cancer Report 2014). Hereditary breast–ovarian cancer syndromes in 5% cases cause BC (Pasche 2010).

Based on their immunohistochemical properties (hormone status), BCs are characterized into three basic types, such as hormone receptor-positive (HR+), human epidermal growth factor receptor 2 positive (HER2+), and triple negative (TN) breast cancers (Marusyk and Polyak 2010). Approximately 85% of all BCs are HR+, and these are mainly associated with estrogen receptor-positive (EHR+)/progesterone receptor-positive (PHR+). HR+ BCs can be further divided into two subtypes: Luminal A and Luminal B. Luminal A tumors tend to be EHR+ and/or PHR+, and HER2-negative (HER2-). Luminal B tumors tend to be EHR+ and/or PHR+, and HER2+ (or HER2- with high Ki67). About 20% of all BCs are HER2+. Triple-negative BCs (basal-like subtype) refers to any BC that expresses other than the genes for ER, PR or HER2. TN BCs account for around 15% of all BC populations. Luminal C, normal breast-like subtype, and transcriptional subtype of TN BC are the other types of BC (Parker et al. 2009; Sotiriou and Pusztai 2009; Lehmann et al. 2011; Masuda et al. 2013). A number of screening tests are known to include detecting BC such as clinical and self-breast exams (e.g. – presence of lumps or other abnormalities), mammography, genetic screening, ultrasound, and magnetic resonance imaging (Screening 2015).

Aim of this review is to note down current circumstances on BC.

2. Genetics in BCs and/or associated symptoms

Mutations in BRCA1 and BRCA2 genes are responsible for BCs of 45-50%. Li-Fraumeni syndrome by mutation in TP53 gene is characterized by early-onset BC along with sarcoma, brain tumors, leukemia, and adrenocortical carcinomas (Li and Fraumeni 1969; Garber et al. 1991). Cowden syndrome is an autosomal dominant condition caused by mutations within the PTEN gene is also characterized by BC (Tan et al. 2012).

Diffuse gastric and lobular BC syndrome is autosomal dominant conditions caused by mutations in the CDH1 gene (Benusiglio et al. 2013). Peutz-Jeghers syndrome, an autosomal dominant condition caused by germline mutations in the STK11 gene has been found a link to BCs (Lim et al. 2004; Hearle et al. 2006). Lynch syndrome is an autosomal dominant, hereditary colon cancer syndrome characterized by right-sided colon cancer, endometrial cancer, ovarian cancer, and other extracolonic cancers (renal pelvis, ureter, small bowel, and pancreas) caused by germline mutations in the mismatch repair genes (MLH1, MSH2, MSH6, PMS2). It is also thought to be linked to BCs (Win et al. 2012a, b).).

Fanconi anemia is a rare autosomal recessive disease manifested by congenital malformations and progressive bone marrow failure. It is manifested by the mutations in BRCAs and PALB2 genes. The latter one is recognized as an important cause of hereditary BCs (Antoniou et al. 2014). Nowadays, mutations in CDH1, PTEN and STK11 genes are also thought to be linked to breast and ovarian cancers (NCCN 2014). Mutations in the CHEK2, ATM, RAD50/51, NBN and NF1 genes have also been implicated in hereditary breast cancer mutations (Offit et al. 2003; Meindl et al. 2010; Golmard et al. 2013).

NFAT transcription factors, especially, NFAT1 (NFATC2) and NFAT5 are implicated in BC. NFAT1 regulates the expression of the TWEAKR and its ligand TWEAK with the Lipocalin 2

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to increase BC cell invasion, while NFAT3 (NFATc4) inhibits Lipocalin 2 expression to blunt the cell invasion. (Fougère et al. 2010; Gaudineau et al. 2012).

3. Treatment strategy

Lifestyle is a major fact about the development of BC. Its modification might prevent 38% of breast cancers in the US, 42% in the UK, 28% in Brazil and 20% in China. Consumption of omega-3 polyunsaturated fatty acids and high soy-based foods may reduce BC (Wu et al. 2008; Zheng et al. 2013). Mastectomy (removal of the whole breast), Quadrantectomy (removal of one-quarter of the breast) and Lumpectomy (removal of a small part of the breast) are the standard surgeries in BC.

HR+ type of BCs can be treated with hormone therapies, including tamoxifen and the aromatase inhibitors, tamoxifen plus everolimus, BOLERO-2, palbociclib, entinostat (a selective histone deacetylase inhibitor), anastrozole, letrozole or exemestane (Aromasin). HER2+ BCs can be treated using anti-HER2 drugs, such as pertuzumab, trastuzumab (Herceptin: arrests G1 phase of cell cyle by binding with mucin 4 (MUC 4), a large membrane-anchored glycoprotein, and the other is CD44/hyaluronan CD44/hyaluronan polymer complex), pertuzumab plus trastuzumab, lapatinib and afatinib (tyrosine kinase inhibitor), T-DM1 (immunoconjugate) and /or trastuzumab, trastuzumab plus taxane, lapatinib/trastuzumab plus capecitabine, and monoclonal antibody (MAb: destroy cancer cells). On the other hand, TN BCs are treated with a combination of surgery, radiation therapy and chemotherapy (Hudis 2007; Parker et al. 2009; Sotiriou and Pusztai 2009; Lehmann et al. 2011; Masuda et al. 2013).

Other treatments in BCs include cytotoxic: sagopilone, cisplatin + vinorelbine + RT, cisplatin + etoposide; targeted: lapatinib + capecitabine vs lapatinib + topotecan and lapatinib + RT (Lombardi et al. 2014). Cyclophosphamide with doxorubicin, docetaxel, methotrexate and fluorouracil are also used in BC. Radiotherapy as external-beam radiotherapy or as brachytherapy (internal radiotherapy) is given after surgery to the region near the tumor bed and regional lymph nodes, to destroy microscopic tumor cells (Massarut et al. 2006; Belletti et al. 2008).

4. Drug resistance and/or overcomes in BCs

Drug resistance is common in all BCs. A tumor could be resistant to multiple treatment strategies, such as for chemo-and MAb resistant (Bianco and Gevry 2012; Vu and Claret 2012; Chen and Sikic 2012). Unfortunately, the underlying mechanisms are yet to be found out. ER+ BCs can be resistant by novo resistance, or acquired resistance (after prolonged utilization of therapy) pathways (Merenbakh-Lamin et al., 2013). Genetic and epigenetic changes (Bianco and Gevry 2012; Nass and Kalinski 2015) are also linked to it. In few studies, D538G or Y537S/C/N mutations have been found in estrogen receptor 1 (ERα). Up-regulation of phosphorylation of PI3K/AKT and down-regulation of protein kinase B (Akt) activity may causes tamoxifen resistance (Miller et al. 2009; Raha et al. 2011). An altered metabolism of tamoxifen may decrease the concentration of active 4-OH tamoxifen (Nass and Kalinski 2015), which may inhibit its activity.

TN BCs resistance to taxanes, anthracyclines, and other chemotherapeutic agents arises from increased drug efflux leading to decreased net intracellular accumulation. Over expression of some multi-drug resistance proteins such as ABCB, MRP, ABCC, BCR, and ABCG are responsible for this type of resistance (Wind and Holen 2011).

P-gp overexpression is evident in un-treated (Leonessa and Clarke 2003) and / or chemo-treated (such as doxorubicin or vincristine, alkaloids, antracyclic antibiotics, podophyllotoxins, taxanes) BCs (Vtorushin et al. 2014; Tang et al. 2015). However, verapamil co-treated with epirubicin down-regulated the levels of P-gp in 48 BCs patients (Mross et al. 1993).

MRP is evident to capture and pump out drugs such as glutathione, glucuronate, sulfate, antracyclic antibiotics, etoposide, vinca-alkaloids, stibium, arsenium, and methotrexate from near the cell membrane as well as from an intracytoplasmic region (Zaman et al. 1994; cole et al. 1994; Paul et al. 1996). Thus, intracellular drug accumulation can be reduced significantly to protect cell survival. LTC4, LTD4 and Sdecylglutathione are the potential candidates of MRP inhibitor (Loe et al. 1996).

ABCG 1, 2, 4, 5, and 8 proteins found are responsible for chemo-resistance (Kerr et al. 2011). Among them, ABCG2 is vastly studied. BCRP has the expression in blood-brain barrier, lactating breast, gastrointestinal tract, placenta, etc. (Jani et al. 2014). Few inhibitors of BCRP are antiviral drugs, tyrosine kinase inhibitors, statins and imatinib, and XR9576 (tariquidar: selective) (Marighetti et al. 2013). However, direct targeting drugs that can selectively inhibit/circumvent ABC-transporters may overcome MDR (Falasca and Linton 2012; He and Wei 2012). Nano-drug technologies such as polymeric/solid lipid/magnetic nanoparticles, liposomes/micelles, dendrimers etc. are employed for this purpose.

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