Chapter 4

PARP INHIBITORS IN THE TREATMENT OF BREAST CANCER

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INTRODUCTION

According to GLOBOCAN 2018, 2.1 million new cases of breast cancer are diagnosed annually worldwide, and breast cancer is one of the four cancer cases among women (1). Most breast cancers are sporadic. 15% of breast cancer has a family history and 5% are responsible for genetic factors. The most common genes that cause breast cancer are known as breast cancer susceptibility gene 1 (BRCA 1) and breast cancer susceptibility gene 2 (BRCA 2) (2). These mutations increase the risk of breast cancer by 10-30 times compared to the risk among women in general population. (3). BRCA1 mutant breast cancers are mostly high grade, triple negative (TNBC) cancer (negative for estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 [HER2]) and basal epithelial phenotype. However, BRCA2-mutant breast cancers more frequently have a hormone receptor positive and luminal B phenotype (4,5). BRCA1 and BRCA2 genes encode proteins involved in cellular response to DNA damage, function as negative regulators in cell cycle, and are active inhibitors of neoplastic progression (6). With the identification of the functions of the BRCA1 and BRCA2 genes, a novel pathway has been opened with poly-adenosine diphosphate [ADP]–ribose polymerase (PARP) inhibitors that targeting tumor cell during DNA repair in genetic breast cancer.

PARP ENZYME, BRCA 1-2 GENES AND SYNTHETIC LETHALITY

Many endogenous or environmental factors cause DNA damage. If this damage is not repaired it results in cell death or cancer-causing mutations. The repair of DNA damage is tightly regulated by a series of interconnected mechanisms. There are two different groups of DNA repair pathways for the repairment of single strand DNA-breaks (SSBs) and double strand DNA-breaks (DSBs). SSBs are repaired by base excision repair (BER), nucleotide excision repair (NER) or mis-

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of the promoter gene (24). BRCA1 / 2 genes can show somatic mutations (25). Mutations in other genes, including DSB repair, may occur (ataxia-telangiectasia mutated [ATM], RAD51, PALB2, Fanconi anemia complementation group [FANC], phosphatase and tensin homolog [PTEN]) (26). There is currently no standardized biomarker for 'BRCAness'. However, this is an active research area. It is unclear whether this dysfunction has therapeutic effects.

Inhibition of PARP is a new treatment for BRCA mutant breast cancer. Studies related to combination therapies with chemotherapy, other targeted therapies and immunotherapies are continuing. New strategies are being studied to generalize the application of PARP inhibitors in BRCA-associated cancers and in some sporadic tumors.

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