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A Study on the Usage of Medications that Interact with the BRCA1 and BRCA2 Genes along with their Efficacy and Side Effects, in the Treatment of Breast Cancer Mutations

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Abstract: ***Background and Objectives: The genes BRCA1 and BRCA2 are crucial for repairing damaged DNA and preventing the development of cancers. It is known that certain gene mutations enhance the risk of getting some cancers, particularly breast and ovarian cancer. Drug interactions directly with the BRCA1 and BRCA2 genes are not well understood, however some medications may be more or less effective in people who have mutations in these genes. The article includes all medications with the potential to interact with the BRCA1 and BRCA2 genes, causing undesirable side effects and drug - induced mutations, as well as medications used to treat breast cancer brought on by a mutation in these genes. Method: We looked for articles published on the strategies for treating substance use disorder in PubMed, Drug - Gene Interaction Database (DGIdb), DrugBankand Google Scholar. We also included quantitative studies of patients receiving breast cancer therapy from community hospitals through different journals. Results: A total of 32 articles are identified of which 22 were full - text reviews, 8 case studies were included and 2 were editorial letters. In which about 17 were on drugs interacting with BRCA1 gene and their adverse effects and treatment regimen and 17 included on drugs interacting with BRCA2 gene and their adverse effects and treatment regimen in breast cancer. It has been found that around 97 drugs have listed to be interacting with BRCA1 gene out of which only few shows clinical application and around 25 drugs have a potential to interact with BRCA2 genes with application to treat breast cancer. Conclusion and Interpretation: The BRCA1 and BRCA2 genes produce proteins that aid in preventing the development of cancers. These genes can be efficiently interacted with by a medication that is used to treat breast cancer. The most commonly utilised pharmacological classes include Immunosuppressants, Hypoxia - Activated Prodrugs (HAP), Alkylating Agents (Cyclohexenes), ATR Inhibitors, and PARP Inhibitors. Additionally, it has been discovered that using oral contraceptives increases the risk of breast cancer because these drugs have been shown to alter the BRCA1 and BRCA2 genes.***

Keywords: BRCA1, Mutation, Breast Cancer, BRCA2, Pharmacogenomics

1. Introduction

BRCA1 and BRCA2 are two genes that are crucial for repairing damaged DNA and preventing the development of cancers. Certain types of cancer, particularly breast and ovarian cancer, are known to be more likely to occur in people who have mutations in certain genes. There isn't much evidence on how pharmaceuticals interact particularly with the BRCA1 and BRCA2 genes, however some medications may work better or worse on people who have mutations in these genes. In the case of people with BRCA1 or BRCA2 mutations, a class of medications known as PARP inhibitors has demonstrated promise in the treatment of breast and ovarian cancer. These drugs work by inhibiting an enzyme involved in repairing damaged DNA, which can cause cancer cells to die. However, some studies have revealed that people with BRCA mutations may respond less favorably to specific chemotherapy medications, such as anthracyclines. Additionally, there may be interactions between some medications used to treat cancer in people with BRCA mutations and those used to treat other medical disorders. It's critical for people with BRCA mutations to talk to their doctor about all drugs and any drug interactions. Your healthcare provider can assist you in understanding how a genetic mutation may affect how you react to particular medications and assist you in selecting the best course of action for your unique circumstances. The medications that may interact with the BRCA1 and BRCA2 genes, which are responsible for breast cancer, are covered in this review study. Drug interactions include their use in the treatment of breast cancer as well as the medications that can result in gene alterations that cause cancer.

2. Methods

A brief discussion of possible pharmacological interactions with the BRCA1 and BRCA2 genes independently is provided in the methodology, along with information on potential side effects and medication treatment plans for treating ovarian and breast malignancies.

1) Drug Interactions with BRCA1 Gene

Drug interactions directly with the BRCA1 gene are not well understood, however some medications may be more or less effective in people who have mutations in this gene. One class of medications, called PARP inhibitors, has demonstrated potential in treating breast and ovarian cancer in people with BRCA1 mutations. These medications function by preventing an enzyme involved in mending damaged DNA, which can result in the death of cancer cells. Olaparib, rucaparib, and niraparib are a few PARP inhibitors. Inhibition of PARP results in the trapping of the PARP - DNA complex at replication forks, causing single - strand breaks to become double - strand breaks (DSBs). PARP trapping and the accumulation of DSBs ultimately leads to cell apoptosis. Cells deficient in BRCA1/2 are particularly sensitive to the effects of PARP inhibition, as cells lacking these functional proteins are unable to repair DSBs, resulting in synthetic lethality. Interaction scores of the PARP inhibitors with BRCA1 obtained from DGIdb are listed for particular drug as; Olaparib (0.52), Veliparib (0.51), Niraparib (0.42), Talazoparib (0.41) Pamiparib (0.21), Rucaparib (0.19). Additionally, the BRCA1 mutation - related breast cancer is primarily RANKL - driven. According to the current study, inhibiting the RANKL/RANK system in BRCA1 mutant mice resulted in mammary glands that were generally normal, as opposed to the control group's invasive carcinomas. Study claims that the drug Denosumab, which blocks the RANKL gene, can prevent genetic breast cancer. An antibody with very minimal side effects, it attaches securely to RANKL and prevents it from acting, preventing genetic breast cancer. According to the findings, the previously licensed medication Denosumab or additional medications in the future that will block RANKL/RANK could be utilized to prevent breast cancer in BRCA mutation carriers. Another class of drug: DNA G - quadruplex stabilizer (CX - 3543) is also proven to show benefit in treatment of breast cancers. G - quadruplexes are four - stranded DNA structures that are over - represented in gene promoter regions and are viewed as emerging therapeutic targets in oncology, as transcriptional repression of oncogenes through stabilization of these structures could be a novel anticancer strategy. An investigational anticancer medication called quarfloxin (CX - 3543) has been demonstrated to have potential action against a number of different cancer types, including breast cancer. A protein termed nucleolin, which is overexpressed in numerous cancer cell types, is the target of quarfloxin's action. Quarfloxin may be active against cancer cells that have BRCA mutations, particularly BRCA1 mutations, according to some research. For instance, a 2011 study in the journal Clinical Cancer Research shown that the drug Quarfloxin was efficient at eliminating breast cancer cells harbouring BRCA1 mutations when administered in vitro (in a laboratory setting). E - 7449, a small molecule inhibitor that is now being investigated as a potential anticancer medicine, is another example of an experimental medication. It is made to specifically target the PARP14 enzyme, which controls gene expression and DNA damage response. E - 7449 has the ability to interfere with the survival and development of cancer cells by inhibiting PARP14. According to certain studies, chemotherapeutic drugs like semustine, also known as methyl - CCNU, have been used to treat various cancers, including brain tumours and lymphomas. BRCA1 and semustine interaction score according to DGIdb is 0.32. Drug interactions with BRCA1 have been observed with other alkylating drugs, such as cyclohexenones. NBS1, SMC1, CHK2, and p53 are among the targets of the medication irofulven and cyclohexane, which also activates ATM. Since irofulven causes DNA double - strand breaks, BRCA1 may influence chemosensitivity through regulating cell cycle checkpoints, DNA repair, and genomic stability in response to irofulven treatment. Tamoxifen is typically given for persons whose breast cancer cells express oestrogen receptors, and it is also thought to be effective in the treatment of breast cancer. Oestrogen receptor positive, or ER positive, cells are those that exhibit this trait. When tamoxifen binds to oestrogen receptors, it prevents oestrogen from binding to those receptors and doing its effect. Thus, the cells cannot be induced to divide and expand by oestrogen. Additionally, bleomycin, a chemotherapeutic drug that is membrane impermeable and reasonably safe when administered extracellularly but highly toxic when administered directly to the cytoplasm. It penetrates the endosomal barrier to deliver bleomycin to the cytoplasm of the Her - 2 overexpressing breast cancer cells.

On the other side, some digs, including oral contraceptives, increase the risk of drug - induced mutations in the BRCA1 and BRCA2 genes. Recent research has shown that oral contraceptives lower ovarian cancer risk in people who carry the BRCA mutation. It is impossible to exclude out a rise in the risk of breast cancer caused by OC. Women with BRCA mutations who are thinking about using OC need to know about possible risk factors for breast cancer and other forms of contraception. OC shouldn't be used in this demographic to prevent ovarian cancer. It has been shown that oestrogen plus progesterone HRT (but not oestrogen alone) increases the risk of breast cancer in women with mutations; however, the effect of oral contraceptive use is unclear. Oral contraceptives temporarily raise the risk of breast cancer in the general population, however the absolute risk is low given that users are often young women. For BRCA mutation carriers, who often acquire breast cancer at an early age, this is not the case. A list of drugs that interact with BRCA1 gene is provided below with their class and interaction score according to DGIdb.

S. No.	Drug Name	Class	Interaction Score
1	Olaparib	ParpInhibitor	0.52
2	Veliparib	Parp Inhibitor	0.51
3	Quarfloxin	Dna G - Quadruplex Stabilizer	0.42
4	Denosumab	Rank Ligand Inhibitor	0.64
5	Irofulven	Alkylating agents	0.42
6	Niraparib	Parp Inhibitor	0.42
7	Talazoparib	Parp Inhibitor	0.41
8	Rucaparib	Parp Inhibitor	0.19
9	Chlorambucil	Alkylating agents	0.11
10	Vinorelbine	Vinca Alkaloids	0.1
11	Tamoxifen	Anti estrogen	0.08
12	Bleomycin	Alkylating agent	0.07
13	Carboplatin	Alkylating agent	0.06
14	Cisplatin	Alkylating agent	0.05
15	Oxaliplatin	Alkylating agent	0.05
16	Emodin	Anthraquinone	0.05

2) Drug Interactions with BRCA2 Gene

An essential part of DNA repair is played by the gene known as BRCA2, which also aids in the prevention of some cancers. Breast, ovarian, and other cancers are more likely to develop when the BRCA2 gene is mutated. According to several studies, HAPs may be useful in treating cancers that have BRCA2 gene abnormalities. In a mouse model of BRCA2 - deficient cancers, a HAP known as TH - 302 was discovered to reduce tumour growth; it is plausible that other HAPs may have a similar effect in people. Chemotherapy medications known as hypoxia - activated prodrugs (HAPs) are made to be activated in low - oxygen locations, such as the interior of solid tumours. This is because, as a result of their rapid growth and limited blood supply, solid tumours frequently include parts that are hypoxic (low on oxygen). HAP selectively inhibited growth of Triple Negative Breast Cancer (TNBC) cell lines under hypoxia. Evofosfamide, a nitroimidazole - linked prodrug of a brominated version of isophosphoramide mustard (Br - IPM) that acts as a DNA cross - linking agent, is selectively activated under hypoxia and has shown antitumor activity. Another HAP drug, PR - 104 is also effective in treatment of breast cancer. However, PR - 104, like all chemotherapy medications, has potential side effects and may not be suitable for all cancer types or people. It will probably take several years before it is made widely accessible for usage, if it is found to be successful. Clinical trials are currently being conducted to assess its safety and efficacy. PARP (Poly ADP - ribose polymerase) inhibitors are a type of targeted therapy that have shown promise in the treatment of cancers with mutations in the BRCA2 genes, The benefits of PARP inhibition have been well characterized in patients who have BRCA1 and BRCA2 mutations in several forms of cancer, patients with cancer with a BRCA mutation have the greatest likelihood of benefiting from olaparib treatment. ATR (Ataxia Telangiectasia and Rad3 - related protein) inhibitors are a type of targeted therapy that are being researched as a potential treatment for cancers with BRCA2 mutations. ATR is a protein that aids in the detection and repair of DNA damage. ATR is particularly crucial for DNA repair in cancer cells that have BRCA2 mutations, and inhibiting ATR activity can cause DNA damage to build up to cancer cell death. ATR inhibitors are made to target cancer cells specifically while preserving healthy cells, potentially reducing adverse effects. Current clinical trials for a number of ATR inhibitors are being conducted on VX - 970, M6620, and AZD6738. Early - stage clinical trials' preliminary findings have indicated promising action in BRCA1 - or BRCA2 - related malignancies, with some patients exhibiting notable tumour reduction. When combined with carboplatin, irinotecan, or olaparib, AZD6738 displayed significant antitumor growth control, whereas tumour regressions can be obtained alone. Chlorambucil is a different medication that has shown promising results in treating BRCA2 mutations. It is specifically toxic to BRCA1/2 - deficient cells, including those that are resistant to cisplatin and olaparib, suggesting the possibility of using chlorambucil clinically to treat conditions that have developed such resistance. Additionally, chlorambucil destroys xenografts that lack BRCA2 and prevents the development of olaparib - resistant patient - derived cancer xenografts (PDTXs). Other Alkylating agents used in treatment of BRCA2 gene mutations are Temozolomide, Cisplatin, Paclitaxel, Cyclophosphamide and Carboplatin. The table below lists the interaction scores for medications that affect the BRCA2 gene.

S. No.	Drug Name	Class	Interaction Score
1	Evofosfamide	Hypoxia - Activated Prodrugs (Hap)	4.95
2	Pr - 104	Hypoxia - Activated Prodrugs (Hap)	4.95
3	Iniparib	Parp Inhibitor	2.47
4	Olaparib	Parp Inhibitor	2.47
5	Veliparib	Parp Inhibitor	1.73
6	Quarfloxin	Dna G - Quadruplex Stabilizer	1.65
7	Talazoparib	Dna G - Quadruplex Stabilizer	1.57
8	Chlorambucil	Alkylating Agents	0.41
9	Temozolomide	Alkylating Agents	0.27
10	Cisplatin	Alkylating Agents	0.1
11	Carboplatin	Alkylating Agents	0.09
12	Everolimus	Immunosuppressant	0.13
13	E - 7449	Parp14 Inhibitor	1.24
14	Berzosertib	Atr Inhibitor	0.27
15	Etoposide	Topoisomerase II Inhibitor	0.1

3. Results

A total of 32 articles are identified of which 22 were full - text reviews, 8 case studies were included and 2 were editorial letters. In which about 17 were on drugs interacting with BRCA1 gene and their adverse effects and treatment regimen and 17included on drugs interacting with BRCA2 gene and their adverse effects and treatment regimen in breast cancer. It has been found that around 97 drugs have listed to be interacting with BRCA1 gene out of which only few shows clinical application and around 25 drugs have a potential to interact with BRCA2 genes with application to treat breast cancer.

4. Conclusion

The BRCA1 and BRCA2 genes produce proteins that aid in preventing the development of cancers. These genes can be efficiently interacted with by a medication that is used to treat breast cancer. The most commonly utilised pharmacological classes include Immunosuppressants, Hypoxia - Activated Prodrugs (HAP), Alkylating Agents (Cyclohexenes), ATR Inhibitors, and PARP Inhibitors. Additionally, it has been discovered that using oral contraceptives increases the risk of breast cancer because these drugs have been shown to alter the BRCA1 and BRCA2 genes.

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