Analyzing and comparing three approaches of treating BRCA mutated Breast cancer: Chemotherapy, Immunotherapy, and PARP inhibitors.

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Abstract

Breast cancer is one of the most common cancers for women across the world. However, the possibility of breast cancer increases with the inheritance of a mutated BRCA1/BRCA2 gene. This mutation increases the chances of cells replicating to form tumor cells and eventually leading to cancerous cells. Even though the mortality rate of breast cancer has been decreasing, there are millions of women being diagnosed with this disease. Thus, this paper analyzes and compares three popular types of therapy for the same: Chemotherapy, Immunotherapy, and PARP inhibitors. Chemotherapy is a common choice of therapy due to its non-specific action and is especially efficient for malignant tumors, but it is associated with various side effects arising from healthy cells being targeted. Immunotherapy, a newer class of therapy, weaponizes the patient's immune system to better recognize and target cancerous cells but is marred with high costs and possibilities of autoimmune diseases. PARP inhibitors, a therapy that specifically targets BRCA mutated cancers, targets the DNA repair pathways and uses synthetic lethality to cause cell apoptosis, but the cancer may develop resistance to it over time. This paper critically evaluates the strengths and limitations of these three approaches, with a focus on their mechanism of action, side-effects, and cost. By comparing these modalities, this paper aims to determine the treatment that would result in the best patient outcomes in those with BRCA mutated breast cancer.

Introduction

Breast cancer is the uncontrolled cell growth in breast tissue due to DNA mutations. One in every three new cancer cases for women assigned females at birth (AFAB) is associated with breast cancer, making it one of the most common cancers (second only to skin cancer). In the United States, there is a 13% chance of the average woman being diagnosed with Breast cancer, however, this statistic significantly increases with certain risk factors. One such factor is the inheritance of the mutated BRCA1 (breast cancer gene 1)/BRCA 2 (breast cancer gene 2) genes, which results in a 45% to 85% chance of the average woman developing breast cancer in their lifetime (John Hopkins Medicine).

In healthy individuals, the BRCA1/BRCA 2 genes (located on chromosome 7 and 13, respectively) facilitate DNA repair through Homologous Recombination (HR) thus playing a vital role in genomic integrity. When these genes are unable to carry out their function, either due to damage or mutation, non-tumorigenic cells may transform into tumor initiating cells, known as Cancer Stem Cells (CSC), which propels the evolution of tumors (Gorodetska et al., 2019)

These mutations have the potential to give rise to numerous types of breast cancers. The most common of which is Invasive Ductal Carcinoma, accounting for 80% of all diagnosed cases, which is marked by the growth of abnormal cells in the milk ducts that have spread to other parts of the breast tissue or have metastasized in the bloodstream or lymph nodes. Other common types of breast cancer include: Invasive Lobular Carcinoma, in which the tumours

originate in the Lobules (milk glands) and spread to other parts of the body; Triple Negative Breast Cancer, accounting for 15% of all breast cancer cases, where the tumor cells lack Oestrogen, Progesterone, and HER2 receptors; Inflammatory breast cancer where the abnormal cells enter the lymph vessels of the breast (National Breast Cancer Foundation, 2024).

The mortality rate of Breast Cancer has been steadily declining since 1989 and is currently 2.5% (American Cancer Society, 2024). This decrease can be attributed to increased awareness, larger funding for research, and the development of a routine screening test (mammography) for more susceptible women, such as those over the age of 40 and those with inherited factors. Despite this decrease, according to the American Cancer Society, predictions for 2024 include 310,720 new cases of breast cancer and 42,250 women will succumb to this disease (American Cancer Society, 2024). Therefore, it is essential to explore the different possible treatment methods and evaluate them holistically to find which will provide better results. Three approaches to treating BRCA mutated breast cancer will be studied: Chemotherapy, Immunotherapy, and PARP inhibitors.

Mechanism of Action

I. Chemotherapy

Chemotherapy, the administration of cytotoxic agents in the body to destroy cancerous cells, is the most common treatment option for all cancer patients. Chemotherapy kills cells as they divide and this may occur in different stages of the cell cycle depending on the type of drug. Some drugs may target the cells during the S phase when DNA is replicating whereas others may target the cells during the M phase to prevent spindle formation, and these interventions trigger cell apoptosis. These drugs are less likely to harm cells that are at rest (NHS). Since cancerous cells grow more rapidly than healthy cells, chemotherapeutic drugs are more likely to destroy cancerous cells, however, this process also kills healthy cells.

Platinum (Pt) based chemotherapy is a common type of chemotherapy, especially
for malignant tumors. Their name is derived from their molecular structure which contains a platinum ion in the center of the molecule. There are three main drugs that come under this category: cisplatin, carboplatin, and oxaliplatin (Zhang et al., 2022). Cisplatin was the first Pt-based therapeutic drug to be approved for medicinal use, and has shown great efficacy in patients. While many chemotherapeutic drugs may be given orally, Cisplatin is injected via the veins for 6-8 hours at a time, every 3-4 weeks (but the exact dosage and time period may vary depending on the type and stage of breast cancer). The general mechanism of action lies in its ability to form cross-links between the double helix of a DNA molecule. This prevents the unwinding of DNA, and subsequently also prevents DNA replication and function. These interstrand crosslinks may only be repaired by HR-based DNA repair, and as mentioned before both BRCA are required for repair via homologous recombination. However, since these cancerous cells lack functioning BRCA1 or BRCA 2 genes, they are “highly sensitive to platinum chemotherapy both *in vitro* and *in vivo*.” (Turner et al., 2012).

II. Immunotherapy

Immunotherapy is a type of biological therapy that utilizes an individual's immune system to treat cancer (National Cancer Institute, 2019). The body's immune system consists of numerous organs and substances that prevent disease and infection by eliminating any foreign substances in the body. However, cancer cells are more difficult targets since they were initially normal cells that eventually mutated. Thus, the immune system may not always recognise cancer cells as foreign. In addition to this, some types of cancer cells may have the ability to avoid destruction via the immune system through numerous mechanisms (American Cancer Society, 2019). One such strategy is taking advantage of the immune checkpoints proteins that exist as switches to "turn on/off" an immune response. To combat this, immune checkpoint inhibitors have been developed to strengthen the immune system so that it is able to destroy tumor cells.

PD-1 (programmed cell death protein 1) is an example of a checkpoint protein on the T cells whose function is to act as an "off switch." The purpose of this is to ensure that the T cells do not destroy the body's functioning and healthy cells. The PD-1 binds itself to PD-L1 (programmed cell death ligand 1), which are found on regular cells. This marks that cell so that the T cells do not attack it. However, some cancer cells have the PD-L1 which provides them with protection against an immune attack (American Cancer Society, 2024). To counter this, monoclonal antibodies have been developed as medicines that act as immune checkpoint inhibitors. They may inhibit the function of either the PD-1 or the PD-L1, and thus, allow the immune system to detect the presence of abnormal cells. Through clinical trials, these checkpoint inhibitors have demonstrated positive responses in breast cancer. (Bedognetti et al., 2016).

III. PARP Inhibitors

PARP (Poly (ADP ribose) polymerase) consists of a large set of enzymes used for DNA repair. This enzyme has the ability to sense any breaks in the DNA and has an established role in repairing Single Strand Breaks (SSBs) (Kanev et al., 2023). These breaks in DNA are very minor and are also fairly common. They are usually caused by DNA replication and environmental stressors, and this break alerts the DNA repair machinery of the break by causing the PARP proteins to catalyze the attachment of long chains of poly ADP-ribose to themselves and other proteins. While PARP is used for minor single strand breaks, the repair for larger, Double Strand Breaks (DSBs) is reliant on the Homologous Recombination (HR) repair by the BRCA genes. However, since those with BRCA mutations are unable to carry out HR due to faulty pathways, the survival of those cells is reliant on PARP enzymes. (Turk et al., 2018).

PARP inhibitors are a set of drugs utilized to block the DNA repair mechanisms of the PARP, making it an effective targeted therapy for breast cancer. Like the name suggests, these inhibitors attach to PARP's catalytic domain, stopping the connection of repair proteins by preventing PARP from establishing PAR chains. Thus, leading to the prevention of repairing SSBs. This invokes synthetic lethality which is when "two conditions that independently would not cause cell death applied in combination." (Chen, 2011). In the case of breast cancer, the repair pathways for both DSBs and SSBs have been compromised through BRCA mutations

and PARP inhibitors respectively. Therefore, resulting in overwhelming damage to the DNA triggering cell apoptosis. Additionally, another mechanism of PARP inhibitors is to “trap” the PARP enzymes on the damaged DNA of the mutated cells. The physical block that is produced by PARP immobilizing on DNA can stop replication forks from progressing during cell division, resulting in more DNA damage. (Murai et al., 2012). Hence, this therapy is effective, as well as very specific to BRCA mutated breast cancer.

Pros and Cons

I. Chemotherapy

Chemotherapy is one of the most popular treatments of cancer, only second to surgery, due to its systematic nature. Unlike other therapies and surgeries that have a localized impact, chemotherapy targets all rapidly dividing cells throughout the body, which include cancerous cells. Hence, it is very effective in cases where the breast cancers have metastasized from their primary tumor. Additionally, this therapy can be implemented to make other treatments more effective. For instance, neoadjuvant therapy (chemotherapy done before surgery) shrinks the tumor so that a less extensive operating procedure may be considered (American Cancer Society, 2019). Conversely, the purpose of adjuvant therapy (chemotherapy done after surgery) is to destroy any remaining cancer cells that are undetectable by imaging scans. This reduces the chances of future recurrence (American Cancer Society, 2019). Additionally, as compared to the other two therapies, chemotherapy proves to be the most cost-effective option at around 48,000 USD for four rounds (Hudson, 2024).

However, there are numerous side-effects associated with Chemotherapy. Due to its non-specific nature, chemotherapy targets all rapidly dividing cells, many of which are non-cancerous. For example, cells in hair follicles and the digestive tract usually divide faster than other cells, which is why chemotherapy is marred by symptoms such as hair loss and diarrhea. Since this therapy also targets healthy cells, it can reduce the number of different types of blood cells: a reduction in red blood cells (erythrocytes) causes anemia and therefore fatigue; a lower count of white blood cells (leucocytes) results in higher chance of infections; a reduced number of platelets brings about easily bruised skin and bleeding gums (NHS, 2023). Additionally, there is also a risk of this therapy inducing infertility in patients due to damage in either their nervous system or pelvic reproductive organs (Waimey et al., 2015). However, the most life-threatening side-effect of chemotherapy is Tumor Lysis Syndrome (TLS). Apoptosis of cells releases nucleic acids, phosphorus, and potassium, which the body usually excretes, but, sometimes cancer cells are destroyed faster than the body can metabolize their cell contents. Thus, TLS may lead to renal failure or cardiac arrest (NHS).

II. Immunotherapy

Immunotherapy is one of the latest and most cutting edge therapies implemented on cancer patients. Its primary advantage comes from its specificity: it manipulates the immune system to recognize cancerous cells so that they can destroy the cancer on its own, thus it does not have any scope to harm healthy cells (Tan et al., 2019). Additionally, the strengthening of the immune system “trains” it to recognize cancer cells in the long term, without the continuous

administration of drugs, promoting the possibility of “long-term cancer remission.” Furthermore, since immunotherapy does not directly interact with the mutated cells, the side-effects of this therapy are extremely low, especially when compared to chemotherapy. Checkpoint inhibitors are also extremely beneficial for a particular type of breast cancer, Triple-Negative Breast Cancer, which is generally hard to treat with other treatments, and also breast cancers that have developed resistance to other drugs. Lastly, immunotherapy is great at working synergistically with other forms of more traditional cancer treatments such as chemotherapy and radiation therapy (Tan et al., 2019).

Despite immunotherapy having its share of advantages, it also has numerous disadvantages. For most patients, the price of immunotherapy exceeds 100,000 USD, and this amount increases with newer therapies (Schaft et al., 2023). Thus, this therapy may be inaccessible to the general public due to its extremely high costs. Additionally, while temporary, there are some side effects associated with administering the medicine which includes pain and swelling at the site of the needle and flu-like symptoms. More serious side-effects can include inflammation of vital organs and glands such as the heart, pituitary gland, kidney and liver, which eventually impairs their function. (National Cancer Institute, 2022). The most common severe effect associated with immunotherapy is the possibility of autoimmune reactions. The purpose of immune systems checkpoint is to ensure that the immune system does not accidentally destroy healthy cells, however, checkpoint inhibitors remove this “safety precaution.” This increases the chance of autoimmune diseases where the immune system can destroy the body’s own and vital cells. (American Cancer Society, 2021). Lastly, only 20% - 40% of patients respond to this treatment (City Of Hope, 2024). This may have two underlying reasons. The first is that those who do not respond to immunotherapy have a lack of functioning T-cells to achieve a response, even when they are activated. Secondly, those who respond well to the treatment were found to have large amounts of CD5+ dendritic cell (a type of immune cell), suggesting that it plays a significant role in the immune system.

III. PARP Inhibitors

PARP Inhibitors are designed in a manner to be extremely specific to BRCA mutated cancers (either ovarian or breast cancer). This is because its mechanism of action relies on the HR being damaged. This highly specific approach ensures that no healthy cells are harmed during treatment. Hence, there is a very small number of side effects associated with PARP inhibitors. Moreover, since this method eliminates the cancerous cells, it has potential for long term benefits. More importantly, the results of a meta-analysis conducted by Sun et al in 2021 yielded that “Progression-Free Survival (PFS) and Overall Survival (OS) were significantly improved in germline BRCA-mutated breast cancer patients with PARP inhibitors” across 1540 patients. In terms of administration of the drug, Olaparib is taken orally as a pill (MD Anderson Cancer Center, 2024). As compared to intravenous injections or intravenous drip which requires numerous trips to the hospital, Olaparib is able to provide a convenient solution for the patients so that they can somewhat maintain their normal routine.

On the other hand, DNA damage of regular cells also depends on PARP. Thus the inhibition of its function may lead to an accumulation of damaged DNA in the body. For example, DNA

damage in the hematopoietic stem cells in the bone marrow may lead to a reduced production of red blood cells, which will lead to anaemia and related symptoms like fatigue. This is evident because among patients taking Olaparib, 45% developed severe anaemia and as a result, 94% had to discontinue the drug (Shiraishi et al., 2023). In addition to these side effects, PARP inhibitors also prove to be an expensive drug with a median price of 13,000 USD to 14,000 USD per month (Liang et al., 2020). While this remains lower than the price for immunotherapy, it is still higher than chemotherapy. Additionally, continuous administration of PARP inhibitors may lead to the cancer cells becoming resistant to it due to selective pressures. They do this through reverse mutations, where the cancer cells are able to restore the function of the BRCA gene by reversing the frameshift mutations. Hence, inhibiting the PARP pathway will not impact cancerous cells since they can rely on their functional HR pathway (Giudice et al., 2024).

	Advantages	Disadvantages
Chemotherapy	1. Systemic nature 2. Effectiveness with surgery 3. Comparatively low costs	1. Targets healthy cells 2. Reduces number of blood cells 3. Risk of infertility 4. Tumor Lysis syndrome
Immunotherapy	1. Specificity 2. Long term cancer remission 3. Works for cancers that have developed resistance 4. Synergistic effect	1. High price 2. Infusion reactions 3. Inflammation of organs and glands 4. Possibility of autoimmune reactions 5. Only a low percent of people respond to treatment
PARP inhibitors	1. Most specific to BRCA mutated breast cancer 2. Reduced side effects 3. Potential long term benefits 4. Studies show that it is effective 5. Can be taken orally	1. Damage to hematopoietic stem cells causing anemia 2. Moderately high cost 3. Risk of resistance due to selective pressures

Table 1: Table describing the benefits and risks associated with the three types of therapy

Conclusion

The three aforementioned cancer treatments are extremely beneficial to eliminating or mitigating cancerous cells from the human body, especially in the case of BRCA mutated breast cancer. If the three treatments are compared, PARP inhibitors would be the most effective for this participant strain of cancer. This is due to the fact that its nature is highly specific to BRCA mutated breast cancer and is also very convenient for the patients to ingest. Furthermore,

numerous studies indicate that the therapy has high progress free survival and overall survival rates. Immunotherapy is a close second because it does not create a dependence on the drugs and is helping the body become more efficient at recognising and destroying the cancer cells. Since this therapy does not directly impact the mutated cells, the side effects are minimal as compared to the other two therapies. However, this does not indicate that chemotherapy is not useful for the treatment of cancer. It is an extremely important therapy which may be used alongside either immunotherapy or PARP inhibitors, which results in less rigorous cycles of chemotherapy. This would reduce the side effects which are the main limitation of this therapy. While each of them have their advantages and associated disadvantages, their mechanism of action demonstrates that they all use efficient, albeit different strategies, to treat cancer.

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