Design Brief

Potential improvements to poly-ADP ribose polymerase (PARP) inhibitors for treating ovarian cancer*

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Reviewed on 4 May 2024; Accepted on 10 June 2024; Published on 26 October 2024

Ovarian cancer continues to be one of the most difficult types of cancer to treat. Medical professionals suggest the use of targeted therapy in the form of a poly-ADP ribose polymerase (PARP) inhibitors to treat ovarian cancer. PARP is a naturally occuring set of proteins that assists with DNA repair and genome stability. PARP inhibitors are a class of drugs that can shut down this repair pathway and, in doing so, prevent cancer cells from repairing damaged DNA, ultimately resulting in cancer cell death. These inhibitors are, therefore, an effective therapy in treating ovarian cancer, especially in women with mutations in BRCA1 or BRCA2. However, studies have shown that PARP inhibitors have off-target impacts on blood stem cells that cause a decrease in erythrocyte count and can ultimately lead to anemia, forcing termination of the PARP inhibitor treatment. However, ceasing PARP treatment can result in an increased progression of the cancer. Our research hypothesizes potential improvements that can be made to PARP inhibitors to increase the drug's specificity to only cancer cells, reducing side effects. By addressing the need for improvements to the PARP inhibitor drug, the researchers hope to draw attention to an issue lacking research in order to catalyze safer treatments for ovarian cancer.

Keywords: Ovarian cancer, poly ADP-ribose polymerase inhibitors, BRCA 1 and 2 genes, lymphatic system

Ovarian cancer is the leading cause of gynecologic cancer death. In 2020, 21,750 women in the United States were diagnosed with ovarian cancer (Gorodetska et al., 2019). This disease affects one in 87 women (American Cancer Society, 2024). With this form of cancer, certain cells in the ovary become abnormal and then multiply uncontrollably to form a tumor.

The ovaries are the female reproductive organs in which egg cells are produced. In about 90 percent of cases, ovarian cancer occurs after age 40, and most cases occur after age 60 (Mayo Clinic, 2023). The most common form of ovarian cancer begins in the epithelial cells, which are the cells that line the surfaces and cavities of the body. These cancers can arise in the epithelial cells on the surface of the ovary. However, researchers suggest that many ovarian cancers begin in the epithelial cells on the fringes at the end of one of the fallopian tubes, and the cancerous cells then migrate to the ovary (Mayo Clinic, 2023).

Ovarian cancer is one of the leading causes of cancer deaths among women

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(Figure 1). Despite breast cancer being the most common cancer found in women, ovarian cancer is three times as lethal, with an overall 5-year survival rate of 30 percent (American Cancer Society, 2024; Yoneda et al., 2011). Most women with ovarian cancer are not usually diagnosed until they are already in the later stages. In late-stage ovarian cancer, otherwise known as metastatic cancer, the cancer spreads away from the ovary and to other organs of the body such as the liver and lungs (Cancer Research UK, 2024). The reason ovarian cancer is not caught early is because there are often no symptoms in the early stages. Despite later stages being associated with symptoms, the symptoms can be non-specific such as loss of appetite and weight loss. In most cases, ovarian cancer usually goes undetected until it has spread within the pelvis and the belly, which is the reason ovarian cancer has a mortality rate of 50 percent (Ovarian Cancer Research Alliance, 2024).

Population impacted by ovarian cancer

Mutations in the breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) genes lead to a higher likelihood of getting ovarian or breast cancer. 2,000 women per year with inherited mutations in the BRCA1 and BRCA2 genes are diagnosed with ovarian cancer (Center for Disease Control and Prevention, 2020).

BRCA1 and BRCA2 genes function

The breast cancer genes 1 and 2, also known as BRCA1 and BRCA2, are critical for cell cycle function. Everyone has 2 copies of the BRCA1 and BRCA2 genes and inherits one set from each parent. When these genes are functioning normally, they act as tumor suppressor genes. BRCA1 and BRCA2 have two main roles that allow them to be tumor suppressor genes.

The first role is the formation of protein structures to navigate a double-stranded break repair. Whenever there is a double-strand break (DSB), BRCA1 and BRCA proteins serve as a base structure to enlist other DNA repair proteins to accumulate at the site of the DSB in order to repair the damage (Gorodetska et al., 2019). The

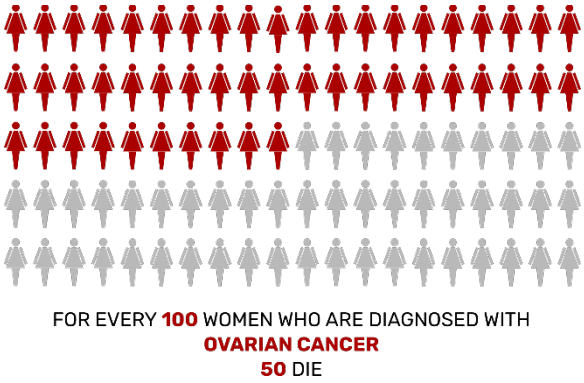

Figure 1. Ovarian Cancer Death Rate.

structure of BRCA1 and BRCA2 mediates homologous recombination, ultimately leading to double-strand break's repair.

The second role of BRCA is the regulation of a cell's life cycle. BRCA1 and 2 control the turnover of the cell cycle. To do this, BRCA1 can induce G1 arrest, barring the cell from entering the S and G2 phase (Gorodetska et al., 2019).

Mutations in the BRCA1 and BRCA2 genes

Due to BRCA1 and BRCA2's high involvement in cell cycle function, a mutation in one of these genes causes extreme complications. Cells are no longer able to stall during G1 and begin to progress through the cell cycle rapidly. Whenever cells are producing a lot of replicants, lots of DNA synthesis occurs, opening up the cell for the possible occurrence of double-stranded backbone breaks. Due to this, BRCA1 and BRCA2 will form protein complexes to help repair these breaks. One of the crucial proteins BRCA will recruit is the enzyme poly (ADP-ribose) polymerase.

Poly-ADP ribose polymerases' role in DNA repair

Poly ADP-ribose polymerases, known as PARPS, are a large family that includes over 18 different enzymes. These enzymes were first discovered in 1963 and named for their ability to "catalyze the transfer of ADP-ribose to target proteins (Morales et al., 2014).

These polymerases play vital roles in DNA repair, chromatin structure, replication, recombination, and transcription. The isoforms of PARPs, specifically PARP1 and PARP2, are the most active in DNA repair, cell proliferation, and cell death. PARP1 and PARP2 are the most well-understood isoforms and will be the main focus of this paper.

When DNA is damaged, PARP enzyme activity increases. In order to repair damaged DNA, PARP has the ability to employ the base excision repair pathway (BER) in response to DNA single-strand breaks (SSBs), ultimately resulting in DNA repair (Chen, 2011).

PARP's capacity to use the BER is why scientists speculated that PARP systems could be used to target cancer cells. If the BER is impaired, this leads to single-stranded DNA breaks turning into double-stranded DNA breaks. When double-stranded DNA breaks occur, the cell becomes reliant on other forms of repair pathways, specifically homologous recombination. However, with cells possessing a deficiency in their ability to carry out homologous recombination such as cancer cells, no DNA repair can occur, ultimately leading to cell death.

PARP inhibitor's role in combating ovarian cancer caused by the BRCA 1/2 mutations

PARP's role in DNA repair led to the creation of a PARP inhibitor to combat cancer. In late 2014, the Food and Drug Administration (FDA) approved the use of PARP inhibitors as a treatment for ovarian cancer (Tew et al., 2020). PARP inhibitors come in pill form, and there are three variations of this drug currently prescribed: olaparib (Lynparza), rucaparib (Rubraca), and niraparib (Zejula), respectively (Cancer Research UK, 2024). These inhibitors are used to combat ovarian cancer because PARP inhibitors are especially able to target cancer cells with the BRCA1 and BRCA2 gene mutations.

PARP inhibitors are used to combat BRCA1 and BRCA2 related cancers due to the BRCA 1/2 and PARP functional interactions (Figure 2). A cell with a mutated BRCA gene has no way to repair DNA double-stranded backbone breaks, so they rely on PARP's repair pathways. PARP inhibitors work by shutting down the BER, resulting in no DNA repair. Then, despite the mutated BRCA gene continuing to rapidly replicate cancerous cells, these cells are being produced with damaged DNA and will quickly die.

PARP inhibitors have become favored over chemotherapy due to their specificity in killing the mutated cancer cells while leaving the non-cancerous cells untouched. Despite the PARP inhibitor's efficiency, more data is beginning to show multiple adverse side effects of these drugs.

The adverse side effects of PARP inhibitors

Hematological toxicities

In certain cases, PARP inhibitors can cause the body to develop new malignancies, which are common with the cancer that the inhibitors previously treated. While PARP inhibitors are very efficient in killing cancerous cells, their continued use tends to result in several hematological toxicities. In a study done in 2022 on the possible toxicities caused by PARPS, it was found that "the outcome of 358 cases (8.76 percent) was death" (Shu et al., 2022). The study highlighted that the olaparib variation had the highest mortality rate of 15.89 percent, causing death in 24 out of 151 of the patients. The hematological toxicities occurred 28 to 30 days after the initiation of the PARP inhibitors, and the authors concluded that the most common cause of PARP death was "modification, interruption, and discontinuation…due to the hematological toxicities" (Shu et al., 2022).

These hematological toxicities occur because of the role PARP enzymes play in cell differentiation and in the formation of erythrocytes (Farrés et al., 2015). A loss of PARP leads to a decrease in the lifespan of a mature erythrocyte, leading to a lower red blood cell count that can eventually lead to anemia.

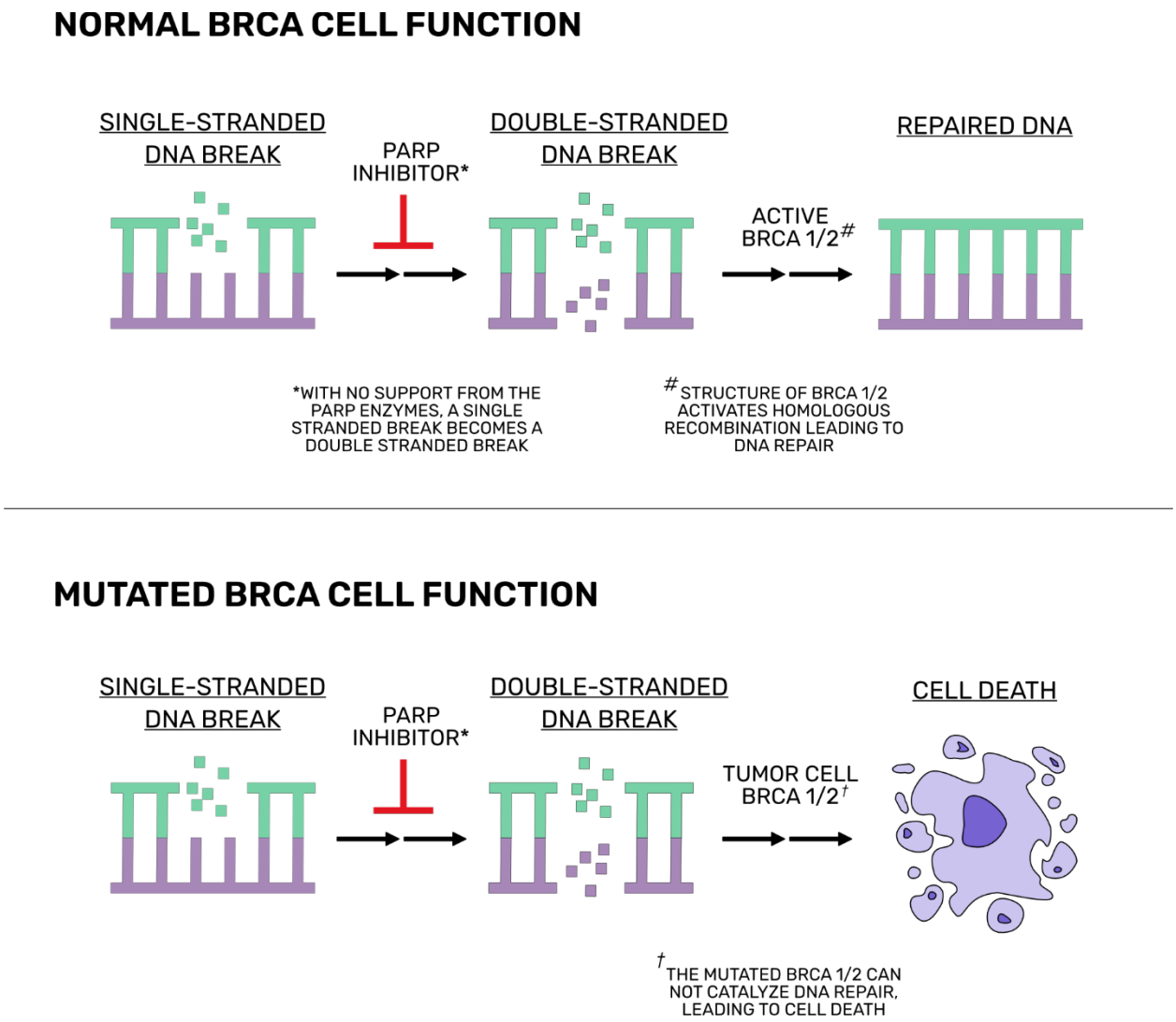

Figure 2. PARP Inhibitor's Interactions with BRCA 1/2.

Impacts on the lymphatic system

While PARP inhibitors are very efficient in killing cancerous cells, continued use tends to result in several hematological toxicities that typically affect the lymphatic system. The most common effects are infections in the lymph nodes, such as lymphadenopathy (the swelling of the lymph nodes), lymphoedema (the swelling of body tissue as the result of lymphatic damage like lymphadenopathy), and lymphatic metastases (the spreading of cancerous cells). The final side effect occurs fairly often as a result of former cancers as well, like the ones that PARP inhibitors are responsible for treating (Shu et al., 2022).

One of the jobs of the lymphatic system is to filter out dead erythrocytes, and severe damage can be caused to the lymph nodes if there are big enough erythrocyte blockages. Most likely, when PARP inhibitors are used as medication, the cancer cells they kill accumulate and block the lymph nodes, leading to the side effects listed above.

Next steps

Hypothesized methods for improving the side effects of PARP inhibitors

Because it is not known exactly how PARP inhibitors cause hematological toxicities and adverse effects on the lymphatic system,

there needs to be more research done in this area. If PARP inhibitors cause a decrease in erythrocytes, then it is crucial to find a ways to target the effects of PARP inhibitors, so that they solely impact cancerous cells.

If there was a way to deactivate the PARP inhibitor or to inhibit the inhibitor in erythrocyte stem cells while still maintaining a downregulation in cancer cells, PARP would be much more effective. It would be possible to create the inhibitor of the PARP inhibitor and inject the medication into the long bones, which are the birth site of erythrocytes. This way, only the erythrocyte stem cells could receive a PARP inhibitor "inhibitor," and the cancer cells could still experience deregulation in PARP. However, due to the PARP inhibitor being a recently discovered drug, there is no research on whether a specific drug exists that could successfully inhibit the PARP inhibitors. More extensive research would need to be conducted to prove the safety and safety and efficiency of this method.

Another solution would be to artificially boost erythrocyte stem cell count while undergoing treatment with PARP inhibitors. This could be done by using a drug such as erythropoietin-stimulating agents. This drug is often used to treat anemia that results from chronic kidney disease and works by stimulating erythropoietin, a hormone that helps to synthesize erythrocytes (Cleveland Clinic, 2022). Erythropoietin-stimulating agents have been found to "directly correct anemia due to low erythrocyte count" (Cleveland Clinic, 2022). Boosting erythrocyte count while using PARP inhibitors as treatment would be a crucial first step in combating the adverse side effects of PARP inhibitors.

There is also the possibility of finding a method of treating ovarian cancer that functions the same way a PARP inhibitor does but without adverse side effects. An article written in July 2023 discussing a selection of potential natural compounds for PARP inhibition presents alternatives to PARP inhibitors as cancer treatments. While this paper focused on PARP inhibitors used to combat glioblastoma, a brain tumor, the findings could be extrapolated to combating ovarian cancer. The article concluded that "ellagic acid and naringin showed a greater interaction trajectory with the PARP than with the PARP inhibitor complex (Rajendran et al., 2023). The article suggested that the use of ellagic acid and naringin, two types of phytomedicines, could be effective PARP-1 inhibitors. However, more research would need to be conducted on whether using ellagic acid and naringin in place of a PARP inhibitor drug would have been successful in targeting ovarian cancer because, at this time, there is no further research on this.

Looking ahead

In 2024, the American Cancer Society estimates that, in the United States alone, 19,680 women will receive a diagnosis of ovarian cancer (American Cancer Society, 2024). About 12,740 of these women will die from it. The malady that is ovarian cancer demands more research, and it is crucial to pour resources into furthering the studies specific to ovarian cancer. By addressing the need for improvements to the PARP inhibitor drug throughout this paper, it is hoped that more attention can be drawn to an issue lacking research in order to catalyze safer treatments for ovarian cancer.

Author contributions

L.A. researched poly-ADP ribose polymerases' impacts on the lymphatic system. Z.K.S. researched BRCA 1 and 2 genes along with their mutations, poly-ADP ribose polymerase as a mechanism in cells, how the function of PARP can be harnessed into PARP inhibitors, and, finally, the possible solutions for improving PARP inhibitor side-effects. L.S. researched the origins of ovarian cancer and the population that is impacted by this type of cancer.

Acknowledgements

In dedicating this research paper to our science teacher, Ms. Minutella, we extend our deepest gratitude for her unwavering dedication to fostering our curiosity and supporting our scientific endeavors Her guidance has been inspiring. We dedicate this research paper with a lot of appreciation. Her

encouragement and guidance have been instrumental in shaping our scientific aspirations, imbuing us with the confidence to embark on this journey. Her unwavering support has been the cornerstone of our academic growth, and it is with immense gratitude that we honor her invaluable contribution to our scientific pursuits.

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