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THE PROFILE AND CLINICAL EVIDENCE OF EFFECTIVENESS OF OLAPARIB IN TRIPLENEGATIVE BREAST CANCER: A REVIEW

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ABSTRACT

Triple-negative breast cancer (TNBC) is one of the most common malignancies in women. The majority of patients with TNBC have a poor prognosis. The main objective of this study is to review the profile and clinical evidence of the effectiveness of Olaparib in treating TNBC. A literature search was conducted using multiple electronic databases, including PubMed, Google Scholar, JSTOR, and Scopus. The search was focused on articles published up to June 2024, ensuring the inclusion of the latest and relevant studies. The primary objective was to investigate the mechanism of action, toxicity profile, resistance mechanisms, and therapeutic effectiveness of olaparib in the treatment of TNBC, regardless of their prior chemotherapy treatment for metastatic breast cancer, prior platinum-based chemotherapy, or usage of cyclin-dependent kinase 4/6 inhibitors (Balmana et al., 2022). The results of this research suggest that the pharmacological efficacy and safety characteristics of this medication in TNBC patients are similar to those reported in the OlympiAD study. Furthermore, stratification of patients for this medication is possible due to the diagnostic techniques that can predict the presence of the BRCA mutation in order to optimize its efficacies. Additionally, developing and validating new biomarkers beyond BRCA mutations for patient stratification could optimize targeted therapy approaches.

INTRODUCTION

Breast cancer is the most prevalent disease seen in women globally, with over 2 million cases documented in the Global Cancer Observatory in 2018 (Bray et al., 2018). 12.8% of women in the United States are expected to receive a breast cancer diagnosis during their lifetime, leading to approximately 42,690 deaths in 2020 (Siegel et al., 2023). Breast cancer can be classified into various types according to their molecular biomarkers; for instance, there are two types: estrogen-positive (ER) and progesterone cancer-positive (PR). Following the identification of both types of cancer that responded to endocrine-based therapy, it became apparent that human epithelial growth factor 2 (HER2) amplification was associated with an unfavorable prognosis for the disease (Howard & Olopade, 2021). As a result of this phenomenon, a monoclonal antibody such as trastuzumab was discovered that is remarkably selective for HER2 overexpression in breast cancer.

In the absence of any biomarkers or single genes expressed on breast cancer cells, there is a possibility that the individual will eventually develop breast cancer. The term for this is Triple-Negative Breast Cancer. Triple-negative breast cancer (TNBC) is characterized by tumors that do not express estrogen-receptor (ER) and progesterone-receptor (PR) as determined by immunohistochemistry, and also do not express human epidermal growth factor receptor 2 (HER2) as discovered by immunohistochemistry or in situ hybridization studies (Howard & Olopade, 2021). From 2012 to 2016, 12% of breast cancer diagnoses in the United States were triple-negative, with a 5-year survival rate

approximating 8% to 16% inferior to that of the subtype with the most favorable prognosis (Giaquinto et al., 2022). Nevertheless, notwithstanding the malignant and fatal propensity of this particular cancer subtype, there exist numerous screening methodologies that can be implemented to personalised treatment approaches and optimize patients' quality of life.

Although the pathophysiology for TNBC is still unclear, there is certain gene in human body that plays important role for the development of breast cancer including TNBC. Tumor-suppressor genes BRCA1 and BRCA2 are implicated in apoptosis, transcriptional regulation, DNA damage repair and recombination, and cell-cycle checkpoint control (Venkitaraman, 2014). Defective DNA repair mechanisms, which are linked to an increased risk of developing breast and/or ovarian malignancies, are induced by mutations in the BRCA genes (Peng et al., 2016). Moreover, according to several studies, BRCA1 mutation (BRCA1Mut) carriers had a higher risk of developing ER-negative/PR-negative breast cancer (Musolino et al., 2007). The modulation of cell cycle DNA repair is dependent on the activity of BRCA genes, which facilitate double-strand DNA breakage via a homologous recombination repair mechanism. It has been demonstrated that basal-like breast cancer, which harbors a mutation in the BRCA1 gene, disrupts this mechanism (Wahba & El-Hadaad, 2015). While the BRCA1 gene does not exclusively govern the mechanism of DNA repair in the human body, the cell can also utilize another gene that encodes an enzyme capable of detecting DNA damage and catalyzing the repair process. The PARP1 gene produces an enzyme that alters several nuclear proteins linked with chromatin. This gene participates in the molecular processes that initiate cellular restoration following DNA damage (Wahba & El-Hadaad, 2015). Initial research indicates that targeting PARP1 for the treatment of BRCA-deficient carcinomas holds great promise. BRCA-mutant carcinomas are exceptionally susceptible to PARP1 inhibitors due to their homologous recombination (HR) repair deficiency and dependence on PARP1-BER for survival (Bryant et al., 2005).

The research aims to review the profile and clinical evidence of effectiveness of Olaparib in triplenegative breast cancer. The research contribution of this study is the comprehensive review and synthesis of the profile and clinical evidence related to the effectiveness of Olaparib in treating triple-negative breast cancer (TNBC). By focusing on this specific cancer type, which is often more aggressive and difficult to treat, the study adds valuable insights into how Olaparib, a targeted therapy, may be utilized in clinical practice. This contribution is significant as it could inform treatment strategies, guide future research, and potentially improve patient outcomes in the management of triple-negative breast cancer.

METHODS

This literature review seeks to examine the characteristics and empirical data about the efficacy of Olaparib in the treatment of Triple-Negative Breast Cancer (TNBC). The method utilized for this study employs a methodical strategy to collect, analyze, and integrate pertinent material, guaranteeing a thorough comprehension of the subject matter. Before starting this review, it was imperative to establish a concise and unambiguous scope and set of objectives. The main aim was to investigate the mechanism of action, toxicity profile, resistance mechanisms, and therapeutic effectiveness of Olaparib in TNBC. The process entailed defining crucial inquiries and domains of interest that the review sought to investigate, such as the drug's effectiveness, negative effects, and patient results. A comprehensive literature search was conducted using multiple electronic databases, including PubMed, Google Scholar, JSTOR, and Scopus. The search was focused on articles published up to June 2024, ensuring the inclusion of the most recent and relevant studies.

Subsequently, the authors created specific criteria for selecting the most pertinent papers, both for inclusion and exclusion purposes. Inclusion criteria encompassed studies that met the following conditions: publication in peer-reviewed journals, availability in English, involvement of human subjects, and explicit focus on the utilization of Olaparib in TNBC. Priority was given to clinical trials, systematic reviews, and meta-analyses due to their superior level of evidence. To ensure the review's relevance and applicability, papers that were unrelated to TNBC, not focused on Olaparib, published in non-English languages, and those that solely involved animal or in vitro research were eliminated. The extraction of data from the chosen studies was carried out using a standardized form to guarantee uniformity and comprehensiveness. The recorded data encompassed essential details such as the design and methods of the trial, patient characteristics, Olaparib dosage and administration, measurable outcomes (including progression-free survival and overall survival), adverse effects, toxicity profiles, as

well as mechanisms of action and resistance. This methodical extraction procedure facilitated a thorough comparison and synthesis of findings across research.

The quality of the studies was evaluated based on particular criteria, including the clarity and precision of the research questions, suitability of the study design, transparency in the methodology, the strength of the statistical analysis, and the relevance and recentness of the study. The quality assessment process guaranteed that only research of high quality was included in the synthesis, so establishing a dependable foundation for the review's results.

The studies were assessed for their quality based on specific criteria, such as the clarity and precision of the research questions, appropriateness of the study design, transparency in the methodology, robustness of the statistical analysis, and the relevance and currency of the study. The quality assessment procedure ensured that only research of high caliber was incorporated into the synthesis, thus generating a reliable basis for the review's findings.

RESULTS

Drug Profile: MOA, Toxicity, and Drug Resistance

Olaparib is one of the drugs that belongs in the targeted therapy class of medication that acts on specific macromolecule and inhibit its function in cancer cells without affecting the normal cells. The mechanism of action of this drug which belongs to the class of PARP1 inhibitor is by competing with NAD+ at the catalytic domain (CAT) of PARP, the formation of PAR polymers is prevented. These effects impair the capacity of cells to recover from DNA SSB damage (Lau et al., 2022). Conversely, unrepaired SSBs have the potential to transform into DSBs via the collapse of the replication fork in the presence of PARP inhibition (PARP entrapment mechanism) (Lau et al., 2022). This finding from the study showed that the DNA could eventually breaks the other strand that can lead to double strand DNA damage. This maybe due to several reasons such as: replication fork collapse, topoisomerase cleavage, oxidative damage, and many more. However, other studies disagree that the DSB converted from SSB is the main cause of cell death in HR-deficient cells (Ström et al., 2011).

As stated previously, HR is a crucial mechanism for repairing double-strand breaks (DSBs) in the DNA that occur during cell replication; however, this pathway cannot function without the BRCA (BRCA1/BRCA2) gene. Biochemical in vitro testing reveals that a PARPi can bind to the PARP-chromatin complex and thereby ensnare the enzyme in an ineffective state at chromatin, or it can bind to the active site of PARP and inhibit its enzymatic activity. For instance, olaparib functions primarily as an active site binder (Zheng et al., 2020). For the illustration of how Olaparib works stated in the Figure 1 below.

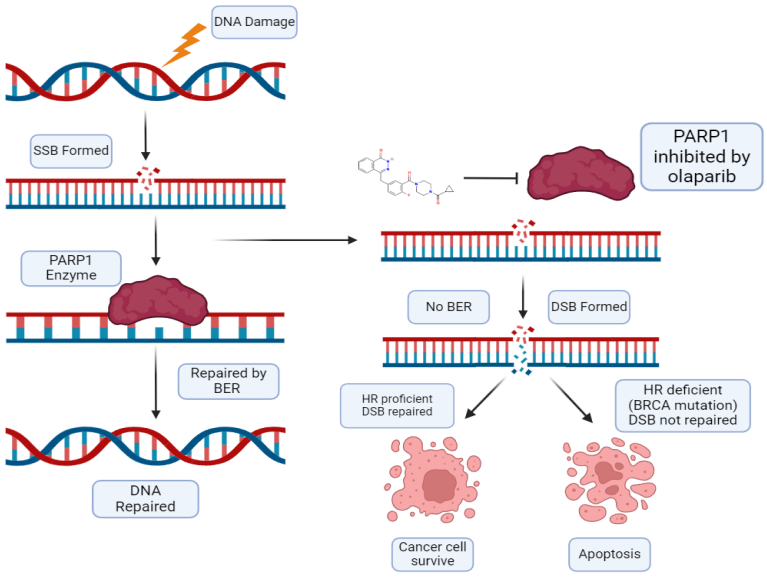

Figure 1. Olaparib MOA. SSB: Single Strand Break, BER: Base Excision Repair, DSB: Double Strand Break. Image generated by Biorender

This mechanism of action demonstrates that the medication was capable of differentiating between cancer cells harboring a mutation in the BRCA gene and normal cells exhibiting normal expression of the gene. Different characteristics of cancer cells have evolved as a result of the process of

evolution. These characteristics are known as "cancer hallmarks," and they are all present in cancer cells. Olaparib can exclusively selectively target cancer cells by interfering with a number of their defining characteristics, such as DNA repair inhibition, which can result in apoptosis and impede the ability of cancer cells to resist cell death.

However, the clinical efficacy of poly ADPribose polymerase inhibitors (PARPis) such as Olaparib in gynecological oncology has been substantially enhanced. Nevertheless, severe organ system toxicity, including that of the hematological system, may be induced by PARPis (Ricci et al., 2020). The label of PARPis includes a warning that the medication may induce anemia, neutropenia, leukopenia, and thrombocytopenia, as issued by the US Food and Drug Administration (FDA) (Guo et al., 2018). Shu et al. (2023) conducted a study to characterized the haematology toxicity of the PARP1is based on real world data. According to their study, A total of 24,045 adverse events (AEs) associated with PARPis were documented, of which 4088 were hematological toxicities and females were more likely to develop the toxicity which is around 82.36%, valid reports in 3522/4088. Acute hematological toxicity AEs were reported most frequently by patients with ovarian cancer (67.98%). Hospitalization constituted the most severe outcome event, accounting for 28.82% of cases, while mortality throughout was 8.76% and Olaparib was the counted of 33.02% of the total reported cases. The list of all form of toxicity are listed in the table 1 below.

Table 1: Case-reported disease of Olaparib toxicity from a study conducted by Shu et al. (2023)

Drug	Disease	Reported Cases
Olaparib	Anemia	606
	Thrombocytopenia	128
	Pancytopenia	111
	Myelosuppression	46
	Myelodysplastic syndrome	184
	Haemolytic anemia	12
	Bone marrow failure	71
	Anemia macrocytic	8

Despite the success of Olaparib as PARP1 inhibitor and its toxicity, the increasing use of this drug also raised the issue of PARP1i resistance. Giudice et al. (2022) identified a number of Olaparib resistance mechanisms exhibited by cancer cells harboring the BRCA1/2 mutation, rendering the cells incapable of executing the DNA repair mechanism. The resistance mechanism depicted in the Figure 2 below.

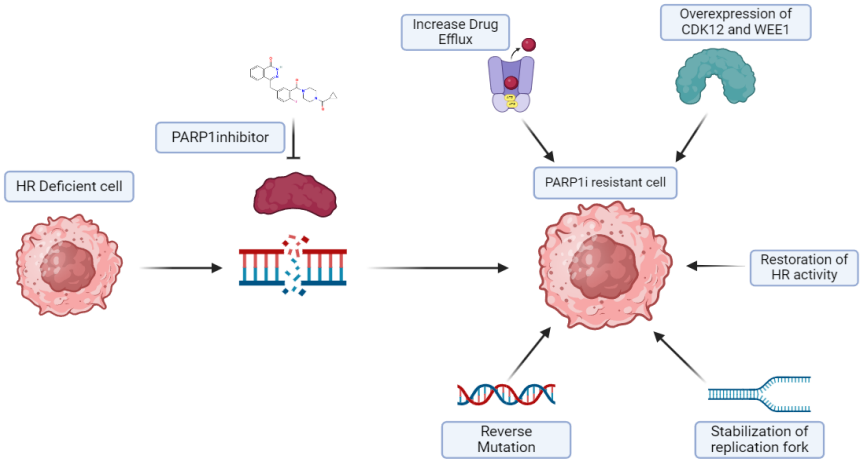

Figure 2. PARP1i (Olaparib) resistance mechanisms. Image generated by Biorender

First, resistance mechanism is restoration of HR activity. The most prevalent acquired PARPis resistance mechanism in HR-deficient cells is the restoration of HR capacity, which can transpire via various mechanisms (Rose et al., 2020). Second, mechanism is by reverse mutation that can lead to PARP1i and platinum analogues resistance. The restoration of BRCA1/2 function is achieved by genetic

mechanisms that result in the deletion of the frameshift, therefore restoring the open reading frame (ORF). This restoration ultimately leads to the creation of a functional protein that is virtually full-length in nature. Moreover, the occurrence of this phenomenon might be attributed to the genetic reversal of the hereditary mutation, so facilitating the restoration of a complete wild-type protein (Lin et al., 2019). Third, is increase drug efflux. The study observed an upregulation of drug-efflux transporter genes (Abcb1a and Abcb1b) responsible for MDR1/P-gp and Abcg2. Abcb1a/b expression in breast cancers increased 2- to 85-fold. This upregulation resulted in an increased rate of drug efflux, leading to enhanced removal of compounds like PARPis from cells (Rottenberg et al., 2008).

Fourth, is by stabilization of the replication fork. In the context of tumor cells lacking BRCA1-2, the nucleases MRE1164 and MUS8165 possess the capability to target the halted replication forks, resulting in the collapse of the forks and subsequent chromosomal abnormalities. In cancer cells, the replication fork in PARP1is resistance cells has been stabilized by some nucleases, leading to the sustained activity of DNA replication (Liao et al., 2018). Fifth, is by alteration in cell-cycle control. Cyclin-dependent kinase 12 (CDK12) and WEE1 are cell-cycle regulators that have a role in the resistance to PARPis by restoring the homologous recombination (HR) process. The mechanism of resistance to PARP1 is attributed to the overexpression of CDK12 and WEE1. CDK12 enhances the activity of DNA repair proteins, while WEE1 is important for arresting the G2-M cell-cycle checkpoint to facilitate DNA repair prior to mitotic entry. WEE1 is highly expressed in several types of cancer, including breast cancer (Bajrami et al., 2014).

Clinical Evidence for Effectiveness

PARP inhibitors have demonstrated encouraging outcomes in the treatment of metastatic triple-negative breast tumors (TNBCs). Study conducted by Im et al. (2020) they conducted a study named OlympiAD randomized trial. The OlympiAD phase III study found that Olaparib tablet 300 mg BID monotherapy provided clinical advantages compared to any chemotherapy treatment chosen by the physician (TPC) for patients with germline BRCA1/2 mutation and human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer. These patients had previously received two chemotherapy lines in the metastatic setting. In this study, they used a population of patient from Asian (China, Taiwan, Japan, and Korea) and found 13.5% (121/895) of them are suspected having BRCA mutation. The efficacy and effectiveness in this study are measured under progression-free survival (PFS). It measured the time The duration of therapy beginning to the point of illness progression or deterioration can serve as a direct or surrogate indicator of clinical efficacy in the context of pharmacological approvals (Hess et al., 2019). In the study, the result for Asian patient population given with Olaparib achieved longer median PFS compared with the chemotherapy chosen by physician (TPC) [22] and this data is consistent with the data collected from global OlympiAD study population (Robson et al., 2017). This means from previous findings, Olaparib monotherapy demonstrated a greater clinical benefit in Asian patients compared to the physician-choice chemotherapy as stated also in the global OlympiAD study.

Another evidence showed in the study conducted by Balmana et al. (2022) using an open-label, single-arm LUCY trial of Olaparib 300 mg BID. The primary objective of this research is to assess the clinical effectiveness and safety characteristics of olaparib in individuals diagnosed with gBRCAm and HER2-negative mBC. The research was carried out in a setting that closely emulates real-world clinical practice, as opposed to the OlympiAD experiment. This research involved the screening of 563 individuals, of which only 256 were included in the analysis of PFS and OS. All patients had a median progression-free survival (PFS) of 8.18 months and an overall survival (OS) of 24.94 months. The findings of this study suggest that Olaparib demonstrates clinical efficacy in all patients who were prescribed it, regardless of their prior chemotherapy treatment for metastatic breast cancer, prior platinum-based chemotherapy, or usage of cyclin-dependent kinase 4/6 inhibitors (Balmana et al., 2022).

Patients Stratification and Diagnostic Tools

Olaparib being sold in the marked as Lynparza with its companion testing called BRCAnalysis and approved by FDA in December 2014. The BRACAnalysis is used to identify patients who may meet the criteria for Lynparza. This permission led to the development of a groundbreaking medication and diagnostic tool that enables patients diagnosed with ovarian cancer or other types of cancer, such as breast cancer, to undergo precise and focused treatment. The BRACAnalysis CDx™ technology is

designed as an in vitro diagnostic tool that aims to qualitatively identify and categorize variations in the protein coding regions and intron/exon boundaries of the BRCA1 and BRCA2 genes (Gunderson & Moore, 2015).

This is achieved by utilizing genomic DNA derived from whole blood specimens that have been collected in ethylenediaminetetraacetic acid. PCR and Sanger sequencing are used to detect single nucleotide variations and tiny insertions and deletions (indels). Multiplex PCR is employed to identify significant deletions and duplications in BRCA1 and BRCA2. BRACAnalysis CDx is the first CDx product designed specifically for gynecologic malignancies, facilitating the identification of suitable patients for the subsequent targeted medication authorized for gynecologic cancers. This marks the advent of a promising age in tailored medication for individuals diagnosed with ovarian cancer, breast cancer, prostate cancer, or pancreatic cancer. It presents prospects for enhancing outcomes and evaluating the extent of HRD loss beyond the BRCA test (Gunderson & Moore, 2015).

CONCLUSION

Triple-negative breast cancer (TNBC) has a poorer prognosis compared to other breast cancer types due to the lack of a biomolecular target. Olaparib and other PARP1 inhibitors have shown promise as targeted therapies, inducing cell apoptosis by causing DNA double-strand breaks. Clinical studies have confirmed the effectiveness of olaparib in treating various cancers, and its efficacy can be optimized by stratifying patients based on BRCA mutation status. Future research should explore combining olaparib with other treatments, assess its long-term effects in diverse patient groups, and identify new biomarkers for better patient stratification and improved outcomes in TNBC.

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