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Efficacy and Safety of PARP Inhibitor in Prostate Cancer: A Systematic Review

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ABSTRACT

Background: Hormone-sensitive prostate cancer (HSPC) and castration-resistant prostate cancer (CRPC) are two distinct forms of prostate cancer that are distinguished by their reactions to hormonal therapy. In general, patients with cancer who seek treatment at CRPC do not survive. The management of CRPC currently involves the use of androgen deprivation therapy (ADT), PC vaccination, chemotherapy, anti-androgen therapy, radionuclide therapy, immunotherapy, and targeted medications, including poly (ADP-ribose) polymerase (PARP) inhibitors. **Objectives**: The objective of this investigation is to determine the safety and efficacy of PARP inhibitors in the treatment of prostate cancer. **Methods**: This study established the adherence to all criteria by comparing it to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 standards. Consequently, the experts were able to guarantee that the research was current. This search strategy considered publications published between 2013 and 2023 in order to obtain these results. This objective was accomplished by employing a variety of online reference sources, including Pubmed and SagePub. Review articles, works that had been previously published, and works that were only partially completed were excluded.**Result**: As a result of our inquiry, we obtained 38 publications from the PubMed database and 173 entries from SagePub. In total, the search yielded 37 articles indexed in SagePub and 54 articles indexed in PubMed for the year 2013. The title screening produced a total of 25 articles for PubMed and 17 articles for SagePub. Ultimately, a total of ten documents were assembled. Five investigations that satisfied the specified criteria were included. **Conclusion**: The safety and efficacy of PARP medications as monotherapy in mCRPC patients with BRCA 1/2 gene mutations or HRR-related gene mutations. As part of an ongoing, comprehensive investigation into PARP inhibitors, over eighty PARP inhibitor therapy trials have been conducted in PC patients, involving a variety of monotherapies and combination regimens.

Keyword: PARP inhibitor, prostate cancer, BRCA 1, BRCA 2.

INTRODUCTION

Prostate cancer is the second most prevalent cancer found in males worldwide. While it is frequently treatable in its first stages, end-stage disease is typically marked by metastatic castrate resistant prostate cancer (mCRPC). In the past ten years, a better comprehension of the fundamental mechanisms of diseases has resulted in measurable enhancements in both the longevity and well-being of patients. Although there have been

significant advancements, the outlook for end-stage disease remains bleak. Multiple groundbreaking treatments have been created for metastatic castration-resistant prostate cancer (mCRPC) in the past ten years. Possible treatment options encompass advanced anti-hormonal drugs, radiopharmaceuticals, chemotherapy, and immunotherapy. These new drugs have helped patients suffering with metastatic castration-resistant prostate cancer (mCRPC) by increasing their prostate-specific antigen (PSA) response and providing a small increase in survival time.[1,2]

Treatments known as poly (ADP-ribose) polymerase inhibitors, or PARPi, target and capitalize on the variations in DNA repair pathways found in malignant tumors. Like healthy cells, cancer cells can sustain DNA damage from internal sources like reactive oxygen species or from external medical interventions like chemotherapy or ionizing radiation therapy. Cell death can occur as a result of a deadly event brought on by severe or cumulative damage. Among the several kinds of DNA damage, double-strand breaks (DSB) are sometimes regarded as the most therapeutically significant variety. Double-strand breaks (DSBs) can result in chromosomal translocations if they are repaired improperly, and if they are not repaired at all, they can induce cell death.[1]

PARP inhibitors exploit abnormalities in DNA repair mechanisms to trigger cellular apoptosis. PARP functions by attaching itself to the site of a single-stranded DNA break in damaged DNA in order to commence the repair process. PARP1 has the ability to repair both single-stranded and double-stranded DNA, not just the former. PARP2 exclusively repairs damaged single-stranded DNA. HR possesses the ability to effectively repair double-stranded DNA that has been damaged. The BRCA1/2 protein is crucial for the process of homologous recombination (HR) repair. Tumor cells harboring BRCA1/2 gene mutations exhibit heightened sensitivity to PARP inhibitors as a result of synthetic lethal processes arising from DNA repair deficiencies. PARP inhibitors can induce apoptosis in cancer cells in people with BRCA gene mutations, thereby functioning as a therapeutic intervention. Ovarian cancer and breast cancer are prone to occur as a result of mutations in the BRCA1/2 gene. Approximately 10% of individuals diagnosed with breast or ovarian cancer possess genetic abnormalities in the BRCA1/2 genes. Furthermore, there have been suggestions of BRCA1/2 somatic mutations occurring in different types of malignancies. As research progresses, the Food and Drug

Administration (FDA) and the European Medicines Agency (EMA) have approved four PARP inhibitors: olaparib, rucaparib, niraparib, and talazoparib.[3,4]

METHODS

Protocol

The author of this study ensured that it adhered to the parameters set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. This is done to assure the accuracy of the conclusions derived from the inquiry.

Criteria for Eligibility

In this literature review, we analyze and differentiate the effectiveness and safety of PARP inhibitors in the treatment of prostate cancer. One can achieve this by conducting research or evaluating the effectiveness and safety of PARP inhibitors in treating prostate cancer. The main objective of this writing is to consistently illustrate the significance of the stated challenges across the entire work.

For researchers to participate in the study, they had to meet the following prerequisites: 1) The manuscript must be prepared in English and should focus on evaluating the effectiveness and safety of PARP inhibitors in treating prostate cancer. For the paper to be eligible for publication, it must satisfy both of these criteria. 2) The examined papers comprise a number of publications that were released after 2013, but prior to the timeframe considered relevant in this systematic review. Studies that are not allowed include editorials, submissions lacking a DOI, already published review articles, and entries that are effectively duplicates of already published journal publications.

Search Strategy

The keywords utilized were "Efficacy and safety of PARP inhibitor in prostate cancer." The systematic review conducted a search for relevant studies using the PubMed and SagePub databases. The search terms used were (("PARP inhibitor"[MeSH Subheading] OR "Prostate cancer"[All Fields] OR "Mechanism of PARP inhibitor" [All Fields]) AND ("Pathophysiology of prostate cancer"[All Fields] OR " Effect PARP inhibitor in prostate cancer"[All Fields]) AND ("Efficacy PARP of inhibitor"[All Fields]) OR ("Safety of PARP inhibitor" [All Fields])).

Data retrieval

The writers conducted an assessment to ascertain whether the study met the inclusion criteria after reviewing the abstract and title of each study. The writers subsequently determined which previous research they wished to incorporate as sources for their article and selected those studies. This conclusion was reached after examining a variety of research studies that all appeared to indicate the same trend. All submissions must be in the English language and must not have been previously viewed.

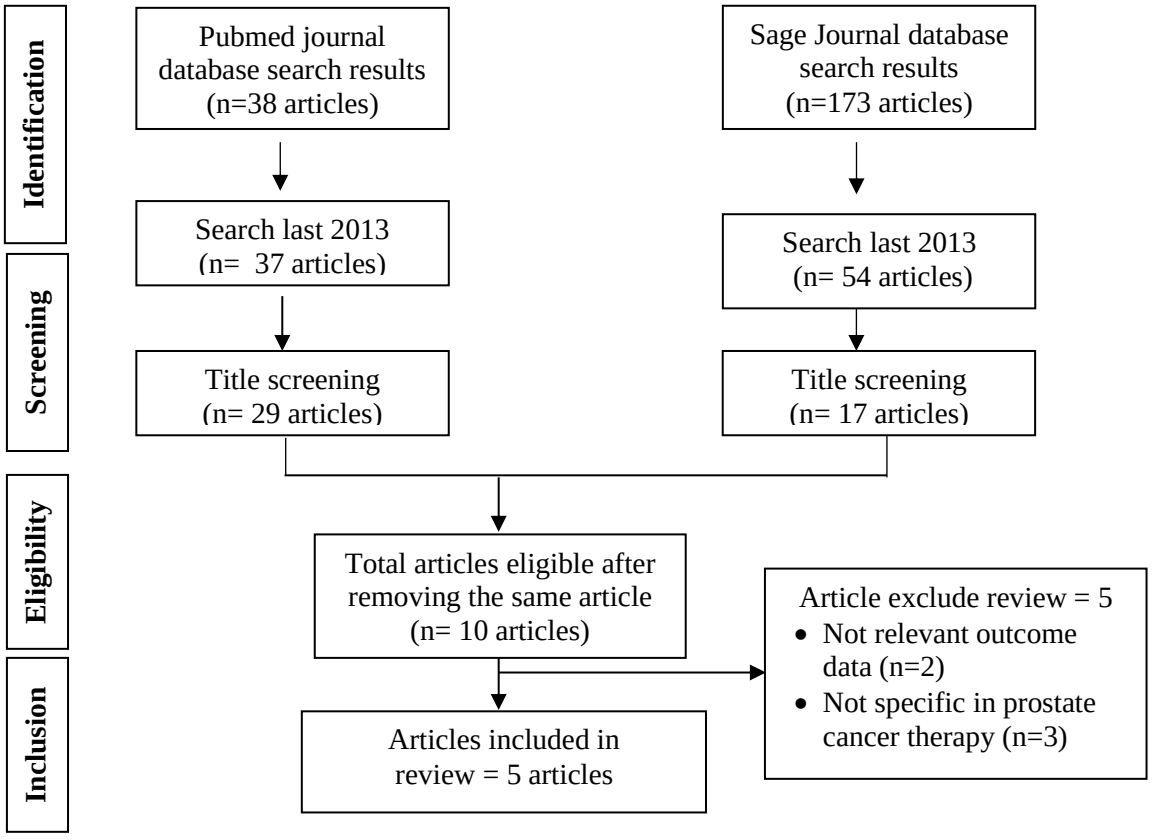

Figure 1. Article search flowchart

The systematic review was limited to papers that met all of the inclusion criteria. This reduces the number of results to only those that are relevant to the search. We do not evaluate the conclusions of any study that does not meet our criteria. Subsequently, the research findings will be thoroughly examined. The inquiry conducted for this research yielded the following items of information: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Before selecting which publications to investigate further, each author conducted their own research on the research presented in the title and abstract of the publication. The subsequent phase will involve the assessment of all articles that are appropriate for inclusion in the review due to their alignment with the criteria laid out in the review. Afterward, we will ascertain which articles to incorporate into the review based on the discoveries we have made. This criterion is implemented during the selection of documents for additional evaluation. in order to simplify the procedure as much as possible when selecting papers to evaluate. The focus of this discussion is on the earlier investigations that were conducted and the characteristics of those studies that justified their inclusion in the review.

RESULT

Our search in the PubMed database yielded 38 publications, whereas our search in SagePub yielded 173 articles. The search conducted for the last year of 2013 resulted in a total of 37 articles for PubMed and 54 articles for SagePub. A total of 29 articles were found in PubMed and 17 articles were found in SagePub throughout the title screening process. Ultimately, we gathered a grand total of 10 documents. We considered five studies that satisfied the criteria.

Chung, JH *et al* (2019)[5] showed In the real-world scenario, routine clinical comprehensive genomic profiling (CGP) found experimental biomarkers for targeted therapeutics in 57% of instances. The inclusion of gLOH and MSI/TMB signatures could provide further information for the selection of poly (ADP-ribose) polymerase inhibitors and immunotherapies, respectively. The study found a correlation between DNA repair

gene alterations (GAs) and genes linked with homologous recombination repair failure, as detected by gLOH. Metastatic site tumors that have a high concentration of GAs can provide valuable insights on potential treatment approaches for metastatic prostate cancer. This study was limited by the absence of a link between clinical outcomes.

Bao, S *et al* (2021)[6] showed Varying toxicity profiles were reported across the various PARP inhibitors. After conducting a comparison of different PARP inhibitors, conventional therapy (chemotherapy), and the combination of PARP inhibitor and angiogenesis inhibitor, it was determined that olaparib is the more secure option. Utilizing findings from this network meta-analysis can enhance the handling of adverse events and alter the prescriptions for PARP inhibitors in the clinical environment. Given the absence of randomized controlled trials explicitly evaluating the safety profile of PARP inhibitors, this report serves as a valuable reference for doctors and researchers. Additional research is required to investigate the comparative attributes of PARP inhibitors.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Chung, JH *et al*., 2019[5]	UK	Prospective study	There were 1,660 tumors at the initial location and 1,816 tumors at the metastatic site, all from different patients.	The most frequently altered genes were AR (23%), TP53 (44%), PTEN (32%), and TMPRSS2-ERG (31%). Recurrent GAs in the RAS/RAF/MEK, phosphatidylinositol 3-kinase, and DNA repair pathways were frequently identified as possible targets. A number of genetic abnormalities (GAs) are involved in the DNA repair pathway,

				including mismatch repair (4%) GAs, CDK12 (6%), homologous recombination repair (23%), and Fanconi anemia (5%). High levels of genomic loss of heterozygosity (gLOH) were shown to be highly correlated with mutations in the BRCA1/2, ATR, and FANCA genes, but were rarely associated with cancers containing CDK12 abnormalities. Tumor mutational burden (TMB) median value was 2.6 mutations per megabase (Mb), which is considered low. Elevated Tumor Mutational Burden (TMB) was seen in 3% of instances, and 71% of these patients also had high Microsatellite Instabilities (MSI). When comparing the 11q13 amplicon (CCND1/FGF19/FGF4/FGF3) and genetic changes (GAs) in AR, LYN,

				MYC, NCOR1, PIK3CB, and RB1, the metastatic site tumors showed a higher concentration than the primary tumors.
Bao, S *et al*., 2021[6]	China	Prospective study	4336 patients	A total of fourteen phase II and III randomized controlled trials, involving a cohort of 4,336 patients, were incorporated in the study. When evaluating adverse events in grades 3–5, olaparib has a higher likelihood (57%) of being a preferable option compared to standard therapy (50%), talazoparib (45%), rucaparib (75%), niraparib (77%), and a PARP inhibitor combined with one angiogenesis inhibitor (94%). Niraparib had an elevated risk for hematological toxicities, while rucaparib demonstrated a higher risk for gastrointestinal toxicities. Talazoparib shown a higher level of

				safety in terms of gastrointestinal function. Olaparib showed a lower incidence of constipation and neutropenia, but an increased risk of anorexia. The concurrent administration of a PARP inhibitor and an angiogenesis inhibitor resulted in an elevated susceptibility to general, metabolic, and gastrointestinal problems.
Bowling, GC *et al.*, 2023[7]	USA	Prospective study, Phase II/III Randomized Controlled Trials	751	A total of eight phase II and III randomized controlled trials (RCTs) were found by the systematic review. In particular, the analysis of anemia comprised eight trials, the analysis of all-grade thrombocytopenia and neutropenia included five trials, and the analysis of high-grade thrombocytopenia and neutropenia included four trials. The use of PARPi was found to be associated with a higher

				incidence of all-grade anemia (RR = 3.37; 95% confidence interval [CI] = 2.37–4.79; p < 0.00001), thrombocytopenia (RR = 4.54; 95% CI = 1.97–10.44; p = 0.0004), and neutropenia (RR = 3.11; 95% CI = 1.60–6.03; p = 0.0008) when compared to a placebo and/or other non-PARPi treatments. Thrombocytopenia and high-grade anemia were found to be substantially associated with an elevated risk, with relative risks of 5.52 and 6.94, respectively. However, high-grade neutropenia did not demonstrate a significant association with the risk. Subgroup stratification analysis revealed variations in both overall and severe toxicity.
Laorden, CER *et al*., 2019[8]	USA	Prospective study	419 patients	For 107 germline DNA damage response (gDDR) mutations, a total of 419

				individuals were screened. 16.2% of them were found to be gDDR mutant carriers, with 6.2% of them having BRCA2, ATM, or BRCA1-specific mutations. In a Spanish database of non-cancer patients, the frequency of gDDR mutations was significantly lower than that of mCRPC patients. The patients with ATM, BRCA1, BRCA2, and PALB2 mutations had a median cancerspecific survival (CSS) of 23.3 vs 33.3 months (p = 0.264), which was 10 months less than the patients without mutations. That difference, though, did not materialise statistically. According to the study, people who had BRCA2 mutations had a significantly worse cancer-specific survival (CSS) (17.4 vs 33.2 months; p = 0.027) than

				people who did not have the mutation. Furthermore, after their first taxane treatment, the prognosis was worse for those with BRCA2 mutations (median cancer-specific survival of 12.8 months versus 23.3 months for non-carriers; p = 0.015). After androgen signaling inhibitor (ASI) treatment, however, there was no statistically significant difference in the prognosis between carriers and non-carriers (carriers had a median cancer-specific survival of 23.3 months compared to 26.2 months for non-carriers; p = 0.215).
Werdt, AV *et al*., 2021[9]	Swiss	Clinical trials	261	Approximately 66% of Icelandic patients with prostate cancer (PCa) who had a family history of BRCA2 mutations had BRCA2 mutations, according to genetic testing. For the first time,

				BRCA2 was associated with PCa, demonstrating a strong correlation between PCa and ovarian or breast cancer. The first PARPi experiment was carried out by Fong et al. in 2009 and focused on patients whose tumours included mutations in BRCA1 or BRCA2. The tumour types included prostate, melanoma, ovarian, breast, and sarcoma. Compared to patients without BRCA mutations, those with the mutation had higher antitumor activity.

Bowling, GC *et* al (2023)[7] showed Poly ADP-ribose polymerase inhibitors (PARPis) are suitable for the treatment of advanced prostate cancer in males. Regrettably, this category of medical treatments has shown the potential for experiencing hematological side effects. We performed a comprehensive examination and statistical analysis of multiple clinical studies with PARPi to further assess the occurrence of side events such as anemia, thrombocytopenia, and neutropenia in patients with prostate cancer. Our investigation revealed a strong correlation between this medication and hematologic suppression. Additional classification indicates that there may be variations among PARP inhibitors within this category of treatment.

Laorden, CER *et al* (2019)[8] showed The survival of individuals with BRCA2 mutations was influenced by the treatment sequence. Specifically, those who received the taxane-ASI sequence had lower cancer-specific survival (CSS) and progression-free survival compared to individuals without the mutation. Nevertheless, there was no discernible disparity in these outcomes between individuals with BRCA2 mutations who received ASI followed by a taxane and those without such mutations.

Werdt, AV et al (2021)[9] show that only 3 out of 25 patients with prostate cancer shown a positive response to the therapy. There was no patient stratification based on genetic changes to determine the most probable responders. There are several reasons why there is increased interest in studying alterations in HRR in PCa. Firstly, HRR mutations are found frequently in various types of cancer, including PCa. Additionally, it is known that individuals with a BRCA2 mutation have a significantly higher risk (8.6 times higher) of developing PCa. Furthermore, BRCA2 mutations are more commonly observed in patients with PCa. Poly(ADP-ribose) polymerase inhibitors (PARPi) have demonstrated clinical advantages in prostate cancer (PCa), breast cancer, and ovarian cancer. Furthermore, other clinical trials are in underway.

DISCUSSION

Poly ADP-ribose polymerase (PARP) enzymes play a crucial role in the repair of single-stranded DNA breaks through base excision. PARP inhibitors (PARPi) have demonstrated the ability to cause synthetic lethality in certain individuals with metastatic malignancies that had germline or somatic mutations in homologous recombination (HR) DNA repair genes. The U.S. Food and Drug Administration (FDA) approved PARPi for widespread use in these particular types of cancers after BRCA1 and BRCA2 underwent substantial research related to breast and ovarian cancer. Recently, the FDA approved two PARP inhibitors—rucaparib and olaparib—for patients with metastatic prostate cancer who have particular genetic mutations in either the BRCA1/2 gene (rucaparib) or one of the 14 HR genes (olaparib).[10,11]

HR proteins are involved in the repair of double-stranded DNA breaks in various ways. Double-strand DNA damage repair is directly facilitated and carried out by BRCA1

and BRCA2, PALB2, and RAD51. Among the members of the HR family that can serve as indicators of double-strand DNA damage are ATM/ATR and CHEK2. They support the following processes, which include the recruitment and activation of BRCA1/2 and other proteins with particular roles. Variations in the degree of sensitivity to PARP inhibition can arise from genetic defects in particular genes involved in homologous recombination (HR) DNA repair, given the distinct roles that these genes play in DNA repair. As a result, it's critical to examine these genetic abnormalities at the gene level.[10,12]

The poly (adenosine diphosphate-ribose) polymerase (PARP)-1 is required for DNA repair due to the DDR gene mutation, and when PARP-1 is inhibited, cancer cells die. PARP inhibitors are used because they are thought to be synthetically deadly. When these drugs are used as first-line treatment for breast tumour patients or as maintenance therapy for patients with pancreatic and ovarian malignancies, survival rates have already shown to increase significantly. Olaparib has been demonstrated to improve overall survival in patients with metastatic castration-resistant prostate cancer (mCRPC) who have a deficiency in homologous recombination repair, even though alternative PARP inhibitors are currently being develop.[13,14]

CONCLUSION

This study examines the effectiveness and safety of PARP inhibitors used alone in patients with metastatic castration-resistant prostate cancer (mCRPC) who have mutations in the BRCA 1/2 gene or other genes related to homologous recombination repair (HRR). The ongoing exploration of PARP inhibitors has not been halted, with more than 80 studies examining the use of PARP inhibitors in the treatment of PC patients. These studies encompass a range of therapeutic approaches, including both monotherapies and combination regimens.

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