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PARP Inhibitors in the Management of BRCA-Positive Prostate Cancer: An Overview

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Abstract: Prostate cancer is the second most common form of cancer in men and the fifth leading cause of death among men worldwide. Men with metastatic castration-resistant prostate cancer (mCRPC) often have BRCA-1 or BRCA-2 gene mutations which can make them sensitive to poly-(ADP-ribose) polymerase inhibitors or PARP inhibitors (PARPi), such as Olaparib, Rucaparib, and Niraparib. Although significant advances have been made with PARPi and the prognosis of patients with mCRPC has improved dramatically, resistance often constitutes a challenge that frequently results in tumor escape. This present communication paper explores the role of PARPi in BRCA-positive prostate cancer and sheds light on numerous published and ongoing clinical trials that will determine the future of PARPi at various tumor stages as a monotherapy or polytherapy regime.

Keywords: prostate cancer; BRCA; PARP; treatment; resistance; inhibitors

Citation: Kourampi, I.; Tsetzan, I.-P.; Kappi, P.; Jain, N. PARP Inhibitors in the Management of BRCA-Positive Prostate Cancer: An Overview. *Uro* **2023**, *3*, 40–47. https://doi.org/10.3390/uro3010006

Academic Editors: Ana Faustino, Paula A. Oliveira and Lúcio Lara Santos

Received: 31 December 2022
Revised: 10 January 2023
Accepted: 16 January 2023
Published: 19 January 2023

1. Introduction

Prostate cancer is the second most common form of cancer in men and the fifth leading cause of death among men worldwide. In 2020 alone, about 1.4 million new cases of prostate cancer were reported globally, accounting for 7.3% of all malignancies in males. The incidence of prostate cancer varies greatly from country to country, especially amongst countries with a high HDI (human development index) and those with a low HDI (37.5 and 11.3 per 100,000, respectively). Geographically, Europe accounts for more than a third of all registered prostate cancer cases, followed by Asia (24%), Northern America (19%), Latin America and the Caribbean (14%) and Africa (4%) [1]. It is predicted that for every 14 years of life, the prevalence of cancer doubles with age, and this proves to be one of the most significant prognostic factors for determining the prevalence of prostate cancer [2]. Furthermore, patients over 65 years old experience an independently higher predictive risk of mortality from prostate cancer [3]. In terms of mortality, the Caribbean has the highest death rate (27.9 per 100,000), while South-Central Asia has the lowest death rate (3.1 per 100,000) [1].

Despite the high incidence rates of prostate cancer worldwide, most cases are identified at an early stage, thus drastically affecting the overall survival rate. Men with a diagnosis of prostate cancer in the US are predicted to have a 5-year survival rate of 98% (all SEER—Surveillance, Epidemiology and End Result stages combined), which rises to almost 100% when the disease is diagnosed at an early stage (localized and regional stages) [4]. The data from the EUROCARE-5 study revealed a life expectancy of fatal cases for patients with prostate cancer aged 65–74 years of 7.7 years, with an overall 5-year survival rate in Europe of 83% [5].

Carcinogenesis is a complex multistage and multistep molecular cascade triggered either by the activation of oncogenes or by the suppression of tumor suppression genes.

These genes are responsible for controlling genome stability, cellular proliferation, and apoptosis. Among those controlling genomic stability, BRCA-1 and BRCA-2 genes are of considerable importance. These tumor suppressor genes are involved in the homologous repair of the double-stranded breaks. Mutations in these BRCA genes can cause genomic instability that leads to the transformation of non-cancerous cells into cancer cells [6].

The type of BRCA mutation that an individual has can play an important role in choosing a personalized and efficient treatment [6]. BRCA-1 is an 1863 amino-acids-long protein with approximately 300 mutations that have been described to date [7]. These mutations predispose an individual to breast, ovarian, and prostate cancer, as well as cancer of the GI tract. The BRCA-2 protein on the other hand, is made of 3418 amino acids, with more than 1800 mutations that have been detected so far. As with BRCA-1 mutations, BRCA-2 mutations are mainly linked to breast, ovarian, and prostate cancer. However other malignancies, such as melanoma, pancreatic, gallbladder, bile duct, and stomach cancers, should also be taken into consideration [6].

2. Methods

For the purposes of this narrative review, we carried out a MEDLINE search for all articles published in the English language using the following terms: "BRCA" and "prostate cancer" and "therapy" or "PARP inhibitor" from January 2014 through November 2022. Relevant articles were searched in the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) annual meetings. We also used relevant data from the American Cancer Society (ACS) website. A total of 144 articles were retrieved and checked for inclusion. From these 144 articles, we deemed 22 articles to be fit for inclusion in the present study (the exclusion of papers was based on insufficient data, papers describing prostate cancer with negative BRCA gene mutation, or lack of clarity about the status of BRCA gene mutation, and other review papers). Trial data was obtained from the U.S. National Library of Medicine's clinicaltrial.gov website (https://clinicaltrials.gov/; accessed 10 January 2023).

3. PARP Inhibitors (PARPi)

Back in 1995, the spread of prostate cancer to the regional lymph nodes was considered end-stage, and radiation was administered, since the function of the PSA (prostate specific antigen) was not yet well understood. With few systemic treatment options available, mitoxantrone was mostly used, a chemotherapy drug for the treatment of androgen independent (hormone refractory) metastatic prostate cancer. The drug gave patients a median survival of fewer than six months [8]. As a result, there have been significant changes in the way that localized prostate cancer is treated, with advancements having taken place in all aspects of therapeutic care. More recently, poly-ADP-ribose polymerase (PARP) inhibitors have dramatically improved the prognosis of patients with metastatic prostate cancer carrying BRCA genes abnormalities. The accumulation of DNA lesions has also been observed to result in a considerable rise in PARP levels in the cells, thereby providing evidence for a crucial role for PARP in DNA repair. When single-stranded DNA breaks occur, base excision repair (BER) is performed by the PARP [9]. The most well-known member of this family of enzymes, PARP-1, is essential for identifying and repairing DNA breaks. When single strand DNA damage is localized, PARP-1 produces poly-ADP-ribose (PAR) and transfers it to acceptor proteins, after which it brings in additional crucial repair enzymes to the damaged DNA spot [10].

Numerous studies have revealed a high correlation between advanced prostate cancer and common deleterious germline mutations in DNA damage repair (DDR) genes, which established the rationale for using PARP inhibitors to treat this condition. Inhibiting PARP should increase the susceptibility of malignant cells to chemotherapy and other therapeutics, since tumor cells with DDR gene mutations depend largely on PARP to repair DNA breaks and mismatches [10]. PARPi act by blocking the enzymes' ability to catalyze reactions and by binding the PARP on DNA at the locations of single-strand breaks [11].

Due to their synthetic lethality, PARP inhibitors are the first-line treatment indicated for the treatment of mCRPC (metastatic castration-resistant prostate cancer) [11].

4. PARPi Clinical Trials

Men with mCRPC often have BRCA-1 or BRCA-2 mutations, which can make them sensitive to poly-(ADP-ribose) polymerase inhibitors or PARP inhibitors (PARPi) [12]. PARP inhibitors are, hence, being investigated in numerous clinical trials for prostate cancer, either as a monotherapy or as a component of combination therapy (Table 1).

Table 1. Clinical trials investigating PARP inhibitors for prostate cancer.

Clinical Trial	Phase	Intervention	Condition/Disease	Recruitment Status	ClinicalTrials.gov Identifier
BRCAAway	II	Olaparib	mCRPC and DNA-Repair Defects	Recruiting	NCT03012321
COMRADE	I/II	Olaparib + Ra 223 dichloride	mCRPC	Recruiting	NCT03317392
GALAHAD	II	Niparib	mCRPC and DNA-Repair Anomalies	Active, not recruiting	NCT02854436
IMANOL	II	Olaparib after docetaxel	mCRPC	Completed	NCT03434158
LuPARP	I	Olaparib + 177Lu-PSMA in mCRPC	mCRPC	Recruiting	NCT03874884
MAGNITUDE	III	Niraparib + Abiraterone Acetate + Prednisone vs. Abiraterone Acetate + Prednisone	mCRPC	Active, not recruiting	NCT03748641
NCT02893917	II	Olaparib + Cediranib vs. Olaparib monotherapy	mCRPC	Active, not recruiting	NCT02893917
NCT03263650	II	Olaparib after Cabazitaxel + Carboplatin	AVPC	Active, not recruiting	NCT03263650
NCT03338790	II	Rucaparib + Nivolumab + Docetaxel or Enzalutamide	mCRPC	Active, not recruiting	NCT03338790
NCT03516812	II	Olaparib + Testosterone	CRPC	Active, not recruiting	NCT03516812
NCT03572478	I/II	Rucaparib + Nivolumab	mCRPC and metastatic Endometrial Cancer	Terminated due to lack of efficacy	NCT03572478
NCT03834519	III	Olaparib + Pemprolizumab vs. Abiraterone Acetate or Enzalutamide	mCRPC	Active, not recruiting	NCT03834519
NCT03840200	I	Rucaparib + Ipatasertib	Advanced prostate, breast, ovarian cancer	Completed	NCT03840200
NCT04019327	I/II	Talazoparib + Temozolamide	Prostate cancer	Recruiting	NCT04019327
NCT04824937	II	Talazoparib + Telaglenastat	mCRPC	Not yet recruiting	NCT04824937
NCT04846478	I	Talazoparib + Tazemetostat	mCRPC	Recruiting	NCT04846478
NiraRad	IB	Niraparib + Radium-223	mCRPC	Completed	NCT03076203
PLATI-PARP	II	Rucaparib + Carboplatin + Docetaxel	mCRPC with homologous recombination DNA repair anomalies	Recruiting	NCT03442556
ProFOUND	III	Olaparib vs. Enzalutamide or Abiraterone Acetate	mCRPC	Active, not recruiting	NCT02987543
PROpel	III	Olaparib + Abiraterone	mCRPC	Active, not recruiting	NCT03732820
QUEST	I/II	Niraparib Combination Therapies	mCRPC	Active, not recruiting	NCT03431350
RAMP	I	RUCAPARIB + other anticancer agents	mCRPC	Active, not recruiting	NCT04179396

Table 1. *Cont.*

Clinical Trial	Phase	Intervention	Condition/Disease	Recruitment Status	ClinicalTrials.gov Identifier
TALAPRO-1	II	Talazoparib	Metastatic Castration Resistant Prostate Cancer and DNA-Repair Anomalies	Active, not recruiting	NCT03148795
TALAPRO-2	III	Talazoparib + Enzalutamide vs. Enzalutamide Monotherapy	mCRPC	Active, not recruiting	NCT03395197
TOPARP A	II	Olaparib	Advanced prostate cancer	Unknown	-
TOPARP B	II	Olaparib	mCRPC and DDR alterations	Unknown	NCT01682772
TRAP	II	Olaparib + AZD6738	mCRPC	Active, not recruiting	NCT03787680
TRITON 2	II	Rucaparib	mCRPC	Completed	NCT02952534
TRITON 3	III	Rucaparib	mCRPC	Active, not recruiting	NCT02975934

Note—mCRPC (metastatic Castration-resistant prostate cancer); AVPC (aggressive-variant prostate cancer); CRPC (castration-resistant prostate cancer); DDR (DNA damage response).

The first PARP inhibitor authorization took place on 15 May 2020 (Figure 1). Rubraca® had been granted FDA approval. Its effectiveness was examined by the TRITON 2 (NCT02952534) clinical trial, which included 115 patients with BRCA-mutated (germline and/or somatic) mCRPC who had received androgen receptor-directed treatment and taxane-based chemotherapy. Rucaparib showed potential benefit in individuals with mCRPC and a germline or somatic BRCA or other DDR gene mutation; 43.9% of these patients experienced an objective response, and 52% reported a documented PSA response. Rucaparib's safety profile was comparable with earlier reports in cases of ovarian and prostate cancer [13].

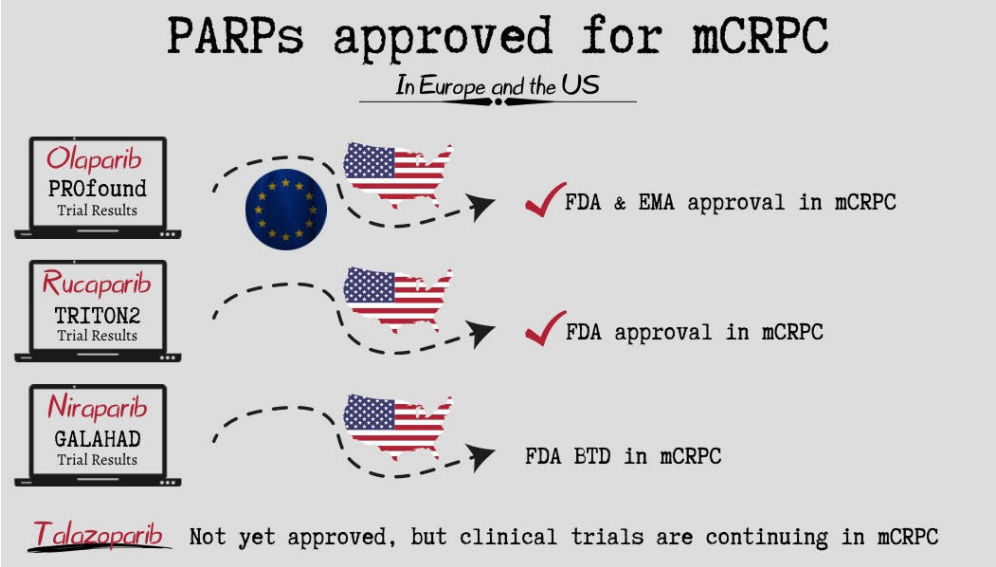

Figure 1. PARP inhibitors approved for the treatment of mCRPC across the globe.

In the ProFOUND study, men with mCRPC who had disease progression despite hormonal treatment were included. This phase III randomized, open-label clinical trial included a total of 387 patients who were divided into two cohorts of 245 patients (cohort A) with BRCA-1, BRCA-2, or ATM mutations and 142 patients (cohort B) having all other DDR gene alterations. Subjects were divided in a 2:1 ratio to take either Olaparib or prednisolone

and an AR signaling inhibitor (enzalutamide or abiraterone) as part of the control group. The primary endpoint was progression-free survival that was proven radiologically. Cohort A had a median duration of overall survival of 19.1 months with Olaparib compared to the control group, which had a median overall survival of 14.7 months (hazard ratio for death, 0.69; 95% confidence interval [CI], 0.50 to 0.97; $p = 0.02$). In cohort B, the median survival was 14.1 months with Olaparib and 11.5 months with the control therapy. In the overall population (cohorts A and B), the corresponding durations were 17.3 months and 14.0 months, respectively. Overall, 66% of the subjects in the control group crossed over to receive Olaparib (56 of 83 patients [67%] in cohort A). A sensitivity analysis that adjusted for crossover to Olaparib showed hazard ratios for death of 0.42 (95% CI, 0.19 to 0.91) in cohort A, 0.83 (95% CI, 0.11 to 5.98) in cohort B, and 0.55 (95% CI, 0.29 to 1.06) in the overall population. Based on the initial findings, the Food and Drug Administration (FDA), in May of 2020, approved Olaparib for mCRPC patients with deleterious HR gene mutations with disease progression following therapy with androgen receptor-signaling inhibitors [14].

A phase II trial called GALAHAD is currently being conducted on 165 patients with mCRPC, 81 of whom had germline mutations (46 BRCA and 35 non-BRCA), and 47% of whom had organ metastases. A total of 300 mg of Niraparib was administered once a day to patients who were included in this trial and whose mCRPC cancer has progressed despite receiving taxane-based chemotherapy and an AR signaling inhibitor as first-line therapy. When compared to patients without BRCA mutations, the findings showed that patients with BRCA-1 or BRCA-2 mutations had a composite rate of 63% whereas those without BRCA mutations had a CRR of 17% [15]. Trials including GALAHAD, MAGNITUDE, and QUEST continue to assess the effectiveness and safety of niraparib in patients with mCRPC and DDR mutations [16]. It is significant to highlight that, whereas the TRITON-1 and ProFOUND studies investigated patients with mono- and bi-allelic mutations, respectively, the GALAHAD study validated patient eligibility with bi-allelic mutations [17].

TALAPRO-1 was an open-label, phase II trial that assessed the efficiency of Talazoparib against mCRPC cancer. Eligibility criteria included men at the age of 18 years old or above, with progressive mCRPC and mono- or bi-allelic alterations of the DDR-HR genes, who received chemotherapy (taxane) and one or more NHT (enzalutamide, abiraterone or both). Eligible individuals received oral Talazoparib (1 mg daily). From October 18, 2017, to March 20, 2020, 128 individuals were recruited, from whom 127 got at least one dose of Talazoparib, and 104 exhibited soft-tissue disease. After 16.4 months, the odds ratio was 29.8% (31/104 patients). The most frequent side effects were anemia (31%), thrombocytopenia (9%) and neutropenia (8%). These results are very convincing and demonstrate a high anti-tumor efficacy for men with mCRPC with DDR-HR gene mutations [18].

The safety profile of PARP inhibitors in patients with mCRPC is of insignificant difference to that in patients with other solid tumors. The most often reported adverse events include fatigue, gastrointestinal side effects, and myelosuppression. The most frequent adverse effects, according to the ProFOUND trial, were nausea (41%), anemia (46%), and fatigue (41%). The drug dosage was reduced in 22% of the patients because of the side effects. Anemia, which occurs approximately in 22% of the cases, is the most frequent adverse effect, according to the GALAHAD and TRITON2 trials [15]. Myelodysplastic syndrome may be linked to PARP inhibitors in combination therapy, according to Nitecki et al., however, this complication is rare. There was no related hepatic or renal impairment, despite frequent elevations in alanine transaminase (ALT), aspartate transaminase (AST), and creatinine [19].

5. Resistance to PARPi

Although PARPi are very effective in everyday clinical practice, the increasing application of these medications in clinical settings has brought up the problem of PARPi resistance [20]. Multiple mechanisms for resistance have been proposed. Firstly, the restoration of homologous recombination (HR) may occur through a variety of different events, including intragenic mutations or the reversion of the epigenome that activates the

open reading frame, thereby restoring the functionality of BRCA-1 or BRCA-2 proteins. Additionally, HR could also be recovered by other DNA repair-related proteins, such as p53-binding protein 1 (53BP1). This protein collaborates with BRCA-1 in balancing the HR and blocks the CtIP-mediated DNA end resection, which promotes DNA repair towards non-homologous end joining (NHEJ). When this protein is under-expressed in the cells that lack BRCA, it draws RAD51 and restores HR. The RAD51 protein is crucial to HR restoration, since it is placed on single and double-stranded DNA with the help of BRCA-2 to create a nuclease-resistant filament that, thus, encourages HR and PARPi resistance [21].

Secondly, an upregulation of ATP-binding cassette (ABC) transporters, which can be caused by the overexpression of the respective genes, is shown to increase the drug efflux and thus reduce the amount of the drug available intracellularly [22]. Thirdly, the accumulation of unrepaired single stranded breaks and the slowed progression of replication forks are significant causes of cell death, and PARPi capacity for PARP trapping exemplifies this. Recent research has shown that the emergence of PARPi resistance is functionally related to the suppression of PARP trapping activity [23]. In tumor samples that were resistant to PARPi, a mutation in PARP-1 (R591C) was frequently noted, which was connected to a decreased PARP-1 trapping action on DNA. In addition, the PAR glycohydrolase (PARG) enzyme participates in PARP-1 trapping action by reverting PARylation to avoid poly-ADP-ribose (PAR) buildup. Loss of the PARG causes cells that have been exposed to PARP to accumulate PAR, which is then used to restore PARP-1-dependent DNA damage signaling. PARP-1 trapping activity is hence reduced, which ultimately leads to PARPi resistance [20].

Fourthly, in halted replication fork protection, BRCA-1 and BRCA-2 genes play a crucial role. The nucleases MRE1164 and MUS8165 can target replication forks that have stalled in tumor cells with BRCA1 or BRCA-2 deficiency, thus leading to fork collapse and chromosomal abnormalities as a result. Some nucleases that can stabilize the replication fork act as a mechanism to prevent DNA replication fork disintegration when PARPi resistance develops. Particularly, the activity of EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) and PTIP (PAX transcription activation domain interacting protein 1-like) at the fork are suppressed in the BRCA-1 or BRCA-2 deficient cells, thereby reducing the recruitment of nucleases and promoting fork protection. Since it is known that PARPi causes unprotected replication forks to degrade, enhanced replication fork stabilization creates resistance to PARPi. Resistance to PARPi can also be mediated by several molecular signaling mechanisms controlling cell division. By being able to stimulate the PARP-1 enzymatic activity (by phosphorylation), the proto-oncogene mesenchymal-epithelial transition tyrosine kinase lowers the binding capacity of the PARPi. A considerable increase in the PI3K/AKT pathway has also been seen after using PARPi, which has the added benefit of promoting cell growth and proliferation. Lastly, the activation of the ATM/ATR pathway is also related to PARPi resistance. It serves as a crucial step in the DNA damage response pathway because it may attract DNA repair complexes by phosphorylating histone H2A. Inhibiting this route might be a future tactic to combat PARPi resistance, because it results in HR restoration [20].

6. PARPi and Immunotherapy

There is mounting evidence that immune checkpoint inhibitors and PARP inhibitors work synergistically. The programed death ligand-1 (PD-L1) plays a role in tumor immunosuppression and is activated in prostate cancer. Thus, suppression of the PD-L1 may enable efficient T-cell activation against cancerous cells. Additionally, PARP inhibition leads to the higher expression of PD-L1 in cells that express BRCA-2 in low amounts. Many ongoing clinical trials combine PARP inhibitors with PD1 blockers, such as pembrolizumab and nivolumab, and PD-L1 blockers, such as durvalumab. According to Karzai et al., mCRPC patients who received a combination of Olaparib and Durvalumab experienced a PSA drop of over 50% in most of the cases, with the median radiographic progression-free survival being 16.1 months as opposed to 4.8 months for those who did not have DDR abnormalities [24].

7. Conclusions

The PARP inhibitors are emerging as very useful treatment modalities in the management of prostate tumors caused by mutations in the HR system. Their use is associated with positive effects, including prolonged survival rates in patients with BRCA-1 or BRCA-2 gene mutations. However, the growing usage of PARP inhibitors in clinical practice sheds light on a rising clinical problem characterized by increasing resistance. There is a need for future studies investigating biomarkers other than BRCA to predict the efficacy of PARP inhibitors, given that the current clinical trials assess the utility and applicability of combination therapy in circumventing PARPi resistance.

Author Contributions: I.K., I.-P.T. and P.K. conceptualized the present paper, while all authors were involved in data collection and the preparation of the manuscript. Supervision was done by I.K. and N.J. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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