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A Comprehensive Review on PARP Inhibitors in Targeted Therapy for Cancers

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Authors' contributions

This work was carried out in collaboration among all authors. All authors contributed to the review design and plan. Authors MG and SK contributed to the data search, collection, extraction, and quality assessment for this review. Authors HP and SSVP created the figure and author MG created the table for the manuscript. All authors wrote the text, reviewed and edited the manuscript, and made substantial contributions to discussions of the content. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The poly (ADP-ribose) polymerase (PARP) family of enzymes involves and regulates various cellular processes and essential functions, such as apoptosis, transcription process, and DNA repair. PARPs (PARP-1, PARP-2, PARP-3) are a branch of familiar proteins that play a crucial role in repairing DNA damage in a human gene involved in different cancers and regulate the base excision repair (BER) pathway. As a target-based drug therapy for cancer, inhibition of PARP stops the PARP-1 and -2 from repairing damaged and mutated DNA in cancer cells, and eventually, the cancer cells die. Considering the limited available therapies for the treatment of advanced and

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recurrent cancers, PARP inhibitors (PARPi) are the first approved cancer drugs that particularly target the response to DNA damage in BRCA (BReast CAncer gene)-1/2 mutated ovarian, pancreatic, prostate, and breast cancers. Recently, six PARPi viz., olaparib, rucaparib, niraparib, talazoparib, fuzuloparib, and pamiparib were approved as monotherapy or in combination with other classes of anticancer agents for the maintenance treatment of advanced or recurrent cancers. Moreover, PARPi appears to improve progression-free survival in women with recurrent platinum-sensitive ovarian cancer as an adjuvant to the conventional treatment. Importantly, the use of PARPi in the management of germline BRCA1/2-associated cancers is a novel therapeutic strategy, representing the first successful targeted therapy in improving outcomes in patients with hereditary cancers. Although resistance to these agents has been reported recently, however, various therapeutic strategies have been employed to overcome resistance and improve the sensitivity of PARPi in the treatment of ovarian, breast, gastric, pancreatic, and prostate cancers.

Keywords: BRCA; fuzuloparib; niraparib; olaparib; pamiparib; PARP; PARP inhibitors; rucaparib; talazoparib.

1. INTRODUCTION

"Poly (ADP-ribose) polymerases (PARP) contain a family of 17 proteins involved in various cellular processes, including stress response, chromatin remodeling, DNA repair, and apoptosis" [1,2]. "In the PARP protein family, these enzymes catalyze the polymerization of nicotinamide adenine dinucleotide (NAD+) intermediates to form an ADP-ribose polymer (pADPr) through transglycosidase activity" [1,3,4]. "The only approach to decide whether a molecule is truly a PARP is to analyze the product of its catalysis as represented to show that pADPr has been synthesized. Based on these criteria, PARP1, PARP2, and tankyrase 1 are true PARPs" [5,6]. "The most well-known and represented member of the PARP protein family is PARP1, which is a ubiquitous nuclear enzyme that utilizes NAD+ to catalyze the addition of ADP-ribose (ADPR) moieties to specific amino acids of target proteins" [1,4]. "It is the most abundant member of the PARP family responsible for about 90% of the polyADPRylation (PARylation) activity in cells" [2,4]. "This enzyme is well characterized and recognized for its function in the early detection and repair of single-strand DNA breaks" [2,4,7]. "Recent research findings indicate that PARP-1 may also play a role in alternative DNA repair pathways, including repair of nucleotide excision, homologous recombination, non-homologous end joining, and mismatch DNA repair" [2,4,6,7].

1.1 Role of PARP-1 in Tumorigenesis and Therapeutic Potential of PARP Inhibitors

In general, PARP-1 recognizes DNA single-strand breaks, is activated, and causes PARP1 auto-PARylation. PARP-1-mediated PARylation recruits various DNA repair proteins to damaged sites [2-7]. Essentially, this mechanism is important for cancer cells to evade cell death leading to uncontrolled growth, abnormal cell proliferation, and tumorigenesis [7-9]. "Inhibition of PARP by synthetic inhibitors competes with NAD+ for the catalytically active site of PARP molecules" [10,11]. "Owing to this, PARP-1 has been widely recognized as a critical therapeutic target for achieving DNA damage-induced cell death in cancer cells by competitive inhibition of PARP. Growing evidence indicates the upregulation of PARP-1 in various cancer cell lines and malignant tumor tissues biopsied from cancer patients" [12-14]. "Notably, PARP inhibitors (PARPi) are successful in the treatment of homologous recombination repair (HR) deficient tumors, representing a novel therapeutic strategy for managing cancers and opening the window for innovative target-based anticancer therapy" [1,15]. "Indeed, targeting PARP-1 employing PARPi has garnered significant attention as a therapeutic target for anticancer therapy. This remarkable consideration has led to an understanding of the molecular pathogenesis of cancer for the contribution of PARP-1 in cell survival and proliferation" [8-10]. "This focused research has made numerous scientific breakthroughs that resulted in drug discovery and the development of several generations of PARPi and subsequently approved for clinical use. Especially, PARPi have been used to target mutated Breast Cancer 1 and 2 (BRCA1 and BRCA2) which are the tumor suppressor genes and tumors with mutations in the essential HR genes" [1,10,16]. "Various PARPi have been approved for the treatment of BRCA-mutated ovarian, breast, and pancreatic cancers" [1-7,10,15-18]. "Additionally, numerous clinical trials registered to investigate the potential of PARPi

as an anticancer therapy in various chemo-resistant cancers" [1,10,15-18].

1.2 Mechanism of Action of PARP Inhibitors

The basic biochemical and molecular mechanism of action by which PARPi produce their anticancer activities has yet to be fully elucidated. A growing body of evidence has remarkably improved the understanding of the pharmacological activity of PARPi and several mechanisms have been recognized [1]. Indeed, PARPi suppresses PARP-1 activity and inhibits the recruitment of DNA repair proteins to the damaged sites. The mechanism of action of PAPRi involves (1) inhibition of single-strand DNA break repair, (2) traps PARP1 at DNA lesions and the trapped PARP-1-DNA complexes cause the collapse of the replication fork, (3) activation of the non-homologous end joining repair pathway, (4) disrupted processing of Okazaki fragments and replication fork speed, (5) disruption of the role of PARP-1 in transcription [1,7,10,19]. Eventually, continuous single-strand DNA (ssDNA) breaks and replication fork collapse lead to double-strand DNA breaks (dsDNA) and are cytotoxic. In general, dsDNA breaks are repaired in homologous recombination-proficient cells. However, homologous recombination-defective cells, such as cancer and nuclear-damaged cells cannot repair dsDNA breaks efficiently and accurately, eventually leading to cell death [10,20-22] This phenomenon is called 'synthetic lethality', a treatment strategy employed in targeted therapies in cancer management, in which the deficiency in the expression of two or more genes results in cell death whereas the deficiency of any specific gene among them does not lead to cell death [21,23]. In cancer cells, this DNA repair mechanism is absent due to a homologous recombination deficiency (HRD), including BRCA1 and BRCA2 mutations, leading to the accumulation of dsDNA breaks and cell death (Fig. 1). This genetic concept of synthetic lethality has been used to establish the efficacy of PARPi and is now considered the first synthetic lethal targeted therapy for the treatment of breast cancer in patients with germline loss-of-function mutations in either BRCA1 or BRCA2 [21-25].

2. CLINICALLY APPROVED PPAR INHIBITORS

Over the past two decades, oncology research has given several scientific advances and breakthroughs in therapeutic approaches to treat cancer propelling several drug discoveries and development. Combining molecular diagnostics, identification of mutations, and biomarkers has harnessed target-based therapies, such as biologicals, immune checkpoints, and small molecule inhibitors targeting oncogenic pathways that account for over 90% of oncology drugs in late-phase clinical development [26-29]. Owing to understanding the molecular pathogenesis of cancer and the importance of PARP in DNA repair for cell survival, several PARPi have been clinically investigated for their therapeutic potential in various cancers. Indeed, targeted therapies, such as PARPi, have greater specificity for binding to PARP1/2, have less off-target side effects than conventional therapies, such as chemotherapy or radiation therapy, and can lead to more favorable outcomes in cancer patients. Moreover, PARPi selectively target tumors with defects in the HR pathway due to BRCA1 or BRCA2 mutations but have little toxicity on normal cells with functional HR. Presently, six PARPi, namely olaparib, rucaparib, niraparib, talazoparib, fluzoparib, and pamiparib have received regulatory approval in many countries for use in cancer treatment and several other PPARi are in various stages of clinical investigation [7,10,15,16,30]. The overview of clinical pharmacology information of the approved PARPi is summarized in Table 1.

2.1 Olaparib

"Olaparib was the first PARPi approved in 2014 by the European Medicines Agency (EMA) and by the Food and Drug Administration (FDA) in the United States. Olaparib was first approved for women with BRCA-mutated (BRCAm) platinum-sensitive relapsed high-grade serous ovarian cancer based on the results from a phase II study" [31]. "The SOLO1 trial examined olaparib as the first-line agent for the maintenance therapy in patients with gBRCA1/2 International Federation of Obstetrics and Gynecology (FIGO) stage III-IV, high grade serious (HGS) or endometrioid ovarian carcinomas after the complete/partial response to initial first-line, platinum-based chemotherapy" [32]. "In 2018, based on the outcome from SOLO2, the EMA approved Olaparib for women with platinum-sensitive relapsed HGSOC regardless of BRCA status" [31]. "The confirmatory phase III SOLO3 study was conducted to evaluate whether olaparib improves outcomes in patients with platinum-sensitive relapsed ovarian cancer and a gBRCAm who have received at least 2 prior lines

of platinum-based chemotherapy" [33]. "Based on the OlympiAD study in the US, olaparib has been approved for the treatment of germline BRCA-mutated metastatic breast cancer" [34]. Moreover, olaparib is currently being tested in a range of tumor types in ovarian, breast, prostate, and pancreatic cancers. Finally, PARPi, including olaparib, may even hold therapeutic potential for treating non-oncological diseases [Table 1; 7,10,30,31].

In proliferating cells, ssDNA breaks are repaired by poly (ADP-ribose) polymerases (PARP) through base excision repair which is critical for survival. PARP inhibition and trapping convert ssDNA breaks to dsDNA breaks and are cytotoxic. In homologous recombination (HR) proficient cells, dsDNA breaks are repaired leading to genome stability and survival during replication. In HR-deficient cells, including breast cancer (BRCA) 1 and 2 mutations, dsDNA breaks are not repaired leading to their accumulation, apoptosis, and finally death [1,2,4,6,7,10,23,25].

2.1.1 Pharmacokinetics

Olaparib is rapidly absorbed, with a peak plasma concentration of 1–3 h post-ingestion and a mean half-life of 6.1 h [35]. It has shown a dose-dependent response rate in chemotherapy in gBRCAm advanced/recurrent triple negative or HR-positive breast cancer [36]. About 80 to 82% of the drug binds to plasma protein and is distributed. The steady-state concentration of the drug is achieved in 3 to 4 days of daily dosing [37]. It is metabolized by CYP enzymes with three major metabolites less active than the original drug [37,38]. The half-life is 5 to 7 h, about 40 to 42% of the dose is excreted via feces, and 44 to 46% is excreted in urine as inactivated metabolites [30,35,37,39].

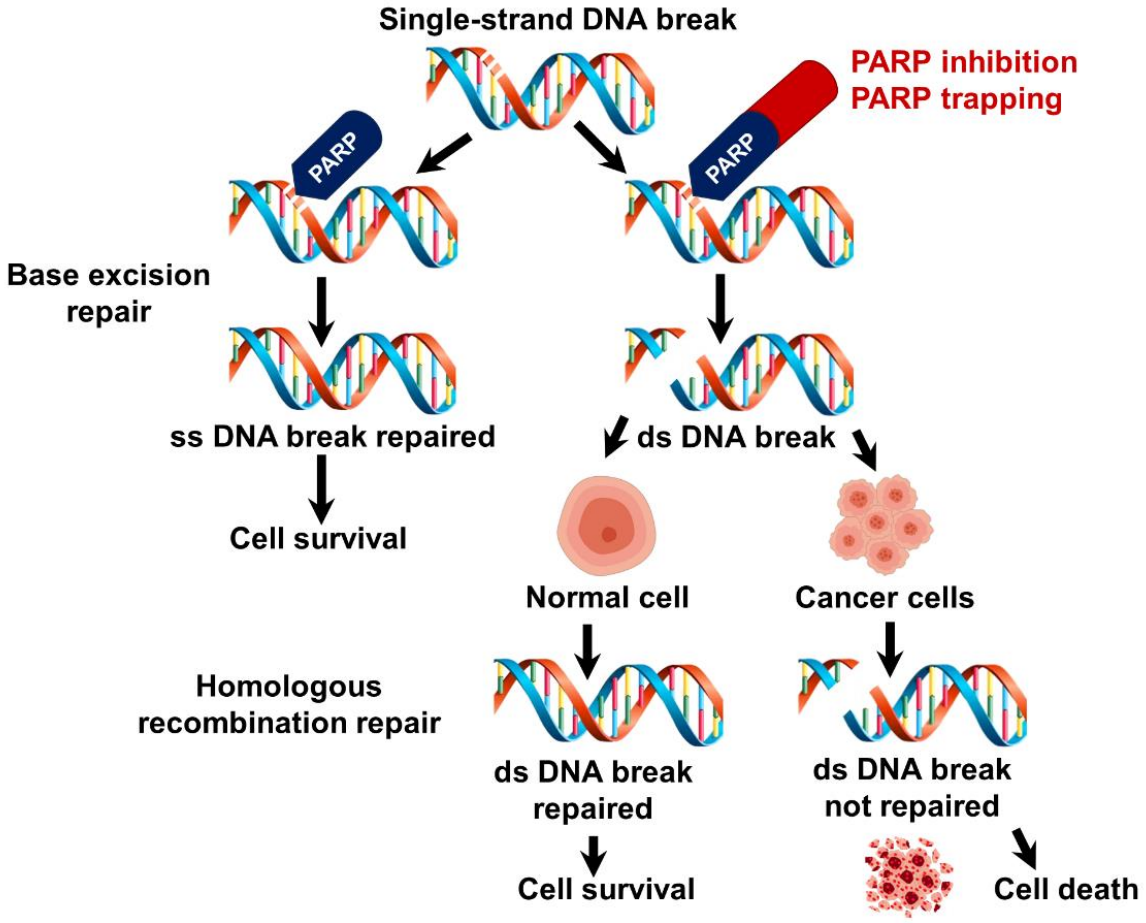

Fig. 1. Mechanism of action of PARP inhibitors

2.1.2 Indication and usage

Ovarian cancer: "This drug is mainly indicated for monotherapy or in combination with bevacizumab for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. It is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy. This is also indicated for the treatment of adult patients with deleterious or suspected deleterious gBRCAm advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy" [35,36,40]. "Olaparib is used in both mono and combination therapies for the treatment of ovarian cancer, such as epithelial ovarian cancer (EOC), advanced ovarian cancer, and BRCA1/2 mutated ovarian cancer. In monotherapy, a single olaparib drug is used twice a day which is used in the early stage of ovarian cancer. In combination therapy, olaparib drug combined with another cytotoxic and targeted therapeutic agent improves the effectiveness of treatment regarding the targeted organ after initial chemotherapy" [7,10,35,41,42].

Breast cancer: This is indicated in patients with deleterious or suspected deleterious gBRCAm, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting [36,43]. This can also be indicated in patients with hormone receptor (HR)-positive breast cancer should have been treated with prior endocrine therapy or be considered inappropriate for endocrine therapy [35,37,43]. "This drug is an effective option for the treatment of advanced or metastatic triple-negative breast cancer that lacks expression of HER2 and HR-negative i.e., lacks estrogen and progesterone receptors" [43,44].

Pancreatic cancer: "This is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen" [37,45].

Prostate cancer: This is for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. This can be used in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious BRCAm metastatic castration-resistant prostate cancer (mCRPC) [37,46].

2.1.3 Dosage and administration

The recommended dose of olaparib is 300 mg (two 150 mg tablets) taken orally twice daily, with or without food, for a total daily dose of 600 mg. The 100 mg tablet is available for dose reduction. 1) In the first-line maintenance treatment of BRCAm advanced ovarian cancer, the treatment should be continued until the disease progresses, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response suggested by no radiological evidence of disease at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the oncologists can be treated beyond 2 years and should decisively derive further benefit from continuous treatment. 2) In the maintenance treatment of recurrent ovarian cancer, treatment should be continued until disease progression or unacceptable toxicity. 3 and 4) In advanced gBRCAm ovarian cancer and gBRCAm HER2-negative metastatic breast cancer, the treatment should be continued until disease progression or unacceptable toxicity [35-38,45].

2.1.4 Adverse effects

The adverse reactions when olaparib is used alone are nausea, vomiting, headache, dysgeusia, cough, fatigue, asthenia, anemia, dyspnea, dizziness, dyspepsia, diarrhea, decreased appetite, neutropenia, leukopenia, and thrombocytopenia. The adverse effects when olaparib is used in combination with bevacizumab were nausea, vomiting, headache, diarrhea, fatigue, asthenia, anemia, lymphopenia, neutropenia, leukopenia, and urinary tract infection. The adverse reactions when olaparib is used in combination with abiraterone and prednisone or prednisolone are nausea, dizziness, fatigue, abdominal pain,

diarrhea, decreased appetite, anemia, and lymphopenia [Table 1; 37,41,42].

2.2 Rucaparib

Rucaparib is a potent small-molecule inhibitor of PARP-1, PARP-2, and PARP-3 that has shown preclinical and clinical activity in ovarian cancer and other types of solid tumors. It was initially developed as rucaparib cammsylate in two formulations, one had the phosphate salt (intravenous [iv] formulation) and the other had camphor sulfonic acid salt (oral formulation) [47,48].

2.2.1 Pharmacokinetics

Rucaparib is orally well absorbed. It can be taken with or without food but has different pharmacokinetic parameters when taken with food (versus fasting) probably due to solubility in the small intestine. The mean fasting half-life is 17 h and the median time to maximal concentration is 1.9 h and can be delayed by 2.5 h after a high-fat meal. However, this moderate food effect on pharmacokinetics is not considered clinically significant [49]. About 70% of the drug binds to human plasma proteins *in vitro*. The drug has a mean apparent volume of distribution of about 2300 L (21%) and is preferentially distributed to red blood cells with a blood-to-plasma concentration ratio of 1.8 [30,50]. In humans, the drug is metabolized in the liver largely through the CYP 2D6 pathway and to a lesser extent by CYP1A2 and 3A4. It is metabolized to form one major oxidative metabolite (M324) and six minor metabolites (M309, M323, M337a, M337b, M337c, and M500). The drug accounted for 45% and 95% of radioactivity in urine and feces, respectively [48,50]. The drug and its metabolites are slowly eliminated from the human body with a half-life of 30.4 and 25.9 h, respectively [51]. The mean apparent total clearance at steady state is 44.2 L/h (45%) and the mean terminal elimination half-life is 26 h (39%) [30,39,48,50].

2.2.2 Indication and usage

Ovarian cancer: It is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy [40,52]. It is also indicated for the treatment of adult patients with a deleterious gBRCAm and/or sBRCAm-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies [48,50**,**53].

Prostate cancer: This drug is indicated for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and taxane-based chemotherapy [46,48,50].

2.2.3 Dosage and administration

The recommended dose of rucaparib is 600 mg (two 300 mg tablets) taken orally twice daily with or without food and continued treatment until the disease progresses or is associated with unacceptable toxicity. For adverse reactions, Dose reduction or interruption of treatment should be considered in case of adverse reactions [50,52].

2.2.4 Adverse effects

The frequently reported adverse reactions are nausea, vomiting, constipation, diarrhea, dyspnea, fatigue, asthenia, anemia, dysgeusia, stomatitis, and nasopharyngitis. The most laboratory abnormalities reported are elevation in creatinine, cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase and reduction in hemoglobin, thrombocytes, platelets, leukocytes, lymphocytes, and neutrophils [Table 1; 50,52,54].

2.3 Niraparib

Niraparib is the third drug in the PARPi series to receive the US FDA approval for cancer chemotherapy. PARPi, such as olaparib and rucaparib have been approved for first-line treatment while niraparib is the first PPARi approved for maintenance therapy of patients with recurrent gynecologic cancers (advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer) regardless of their BRCA mutation and HRD status [55,56].

2.3.1 Pharmacokinetics

This drug is readily absorbed orally with 73% bioavailability in humans. Food is not interfering with pharmacokinetic parameters [30,55]. The maximum drug (83.0%) binds to plasma proteins and the average apparent volume of distribution

(Vd/F) is about 1220 L. In a population pharmacokinetic analysis, the Vd/F of niraparib was 1074 L in cancer patients [57,58]. It is metabolized in the liver and is eliminated primarily through the hepatobiliary and renal routes [59,60]. The mean half-life of this drug is 36 h following multiple daily doses of 300 mg. In a population pharmacokinetic analysis, the apparent total clearance of niraparib was 16.2 L/h in cancer patients [39,57,58,61].

2.3.2 Indication and usage

Ovarian cancer: This drug is indicated in adult patients for the maintenance of treatment of advanced or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy [30,40,57,58]. It is also indicated for the treatment of adult patients who have been treated with three or more prior chemotherapy regimens with advanced ovarian, fallopian tube, or primary peritoneal cancer and whose cancer is associated with positive HRD status in a suspected or deleterious mutation in BRCA or instability of genomic changes and who have progressed more than six months after response to the last platinum-based chemotherapy [40,57,58].

2.3.3 Dosage and administration

The recommended dose of niraparib as monotherapy is 300 mg (three 100 mg capsules) taken once daily orally [57,58]. In first-line maintenance treatment of advanced ovarian cancer for patients weighing less than 77 kg or with a platelet count of less than 150,000/μL, the recommended dose is 200 mg (two 100 mg capsules) taken orally once daily. For patients weighing greater than or equal to 77 kg and who have a platelet count greater than or equal to 150,000/μL, the recommended dose is 300 mg (three 100 mg capsules) once daily taken orally. For the maintenance treatment of advanced ovarian cancer, patients should start treatment with niraparib not later than 12 weeks after their most recent platinum-containing regimen. In the maintenance treatment of recurrent ovarian cancer, the recommended dose of niraparib is 300 mg (three 100 mg capsules) taken orally once daily and the treatment should be started not later than 8 weeks after their most recent platinum-containing regimen. In advanced ovarian cancer treatment after three or more chemotherapies, the recommended dose of niraparib is 300 mg (three 100 mg capsules) taken once daily orally [57,58,60].

2.3.4 Adverse effects

The most common adverse reactions with this drug are nausea, vomiting, abdominal pain/distention, constipation, diarrhea, dyspepsia, mucositis/stomatitis, dry mouth, fatigue, decreased appetite, thrombocytopenia, anemia, neutropenia, leukopenia, palpitations, AST and ALT elevation, myalgia, back pain, arthralgia, headache, dizziness, dysgeusia, insomnia, anxiety, acute kidney injury, urinary tract infection, nasopharyngitis, cough, dyspnea, rash, hypomagnesemia, and hypertension [Table 1; 57,58].

2.4 Talazoparib

Talazoparib, the fourth PARPi approved by the US FDA, is an oral PARPi with potent trapping activity of PARP at damaged sites of DNA [62]. Talazoparib prevents the repair of ssDNA break via the base-excision repair pathway by two mechanisms. First, it inhibits PARylation by mimicking NAD+ in structure and binds to the PARP1/2 catalytic domain. A second and more cytotoxic mechanism is known as PARP trapping, where talazoparib prevents the dissociation of PARP-DNA complexes that are required for PARP-mediated ssDNA break repair. Talazoparib may lead to minor allosteric retention whereas no allosteric retention confers in olaparib, and niraparib, rucaparib, and veliparib lead to allosteric pro-release [63].

2.4.1 Pharmacokinetics

Talazoparib reaches a steady state within 2 to 3 weeks after chronic daily oral administration. The median time to reach C_{max} (T_{max}) is generally between 1 and 2 h after oral dosing. In particular, high-fat, high-calorie food reduces the C_{max} by 46%, the T_{max} is delayed from 1 to 4 h, and AUC_{inf} is not affected following a single oral dose of 0.5 mg. The drug has about 74% protein binding *in vitro* and an apparent volume of distribution (Vd/F) of 420 L [64]. It undergoes minimal hepatic metabolism and urine is the major route of elimination in humans. It is eliminated with a terminal phase half-life of 90 h. Renal impairment has no marked effect on the pharmacokinetics of this drug [30,39,65,66].

Table 1. Approved PPARi drug names, indications, dose(s), and adverse reactions [7,30,35-37, 40,45,46,48,50,55-58, 64-66,71,72,79]

Drug name	Indications	Dose	Adverse reactions
Olaparib	Ovarian cancer, breast cancer, pancreatic cancer, and prostate cancer	100 mg, 150 mg	*Alone*: Nausea, vomiting, headache, dysgeusia, cough, fatigue, asthenia, anemia, dyspnea, dizziness, dyspepsia, diarrhea, decreased appetite, neutropenia, leukopenia, and thrombocytopenia *Combination with bevacizumab*: Nausea, vomiting, headache, diarrhea, fatigue, asthenia, anemia, lymphopenia, neutropenia, leukopenia, and urinary tract infection *Combination with abiraterone and prednisone or prednisolone:* Nausea, dizziness, fatigue, abdominal pain, diarrhea, decreased appetite, anemia, and lymphopenia
Rucaparib	Epithelial ovarian, fallopian tube, or primary peritoneal cancer, and prostate cancer	200 mg, 250mg, 300 mg	Nausea, vomiting, constipation, diarrhea, dyspnea, fatigue, asthenia, anemia, dysgeusia, stomatitis, nasopharyngitis, elevation in creatinine, cholesterol, AST, ALT, and alkaline phosphatase and reduction in hemoglobin, thrombocytes, platelets, leukocytes, lymphocytes, and neutrophils
Niraparib	Epithelial ovarian, fallopian tube, or primary peritoneal cancer	100 mg, 200 mg, 300 mg	Nausea, vomiting, abdominal pain/distention, constipation, diarrhea, dyspepsia, mucositis, stomatitis, dry mouth, fatigue, decreased appetite, thrombocytopenia, anemia, neutropenia, leukopenia, palpitations, AST and ALT elevation, myalgia, back pain, arthralgia, headache, dizziness, dysgeusia, insomnia, anxiety, acute kidney injury, urinary tract infection, nasopharyngitis, cough, dyspnea, rash, hypomagnesemia, and hypertension
Talazoparib	Breast cancer, HRR Gene-Mutated mCRPC prostate cancer	0.25 mg, 0.5 mg, 0.75 mg, and 1 mg	*Alone:* Reduced hemoglobin, neutrophils, lymphocytes, and platelets, elevated glucose, AST, ALT, and alkaline phosphatase, fatigue, nausea, headache, vomiting, alopecia, diarrhea, decreased calcium, and decreased appetite. *Combination with enzalutamide:* Reduced hemoglobin, neutrophils, lymphocytes, platelets, calcium, appetite, sodium, phosphate, magnesium, and potassium; fatigue, nausea fractures, dizziness, elevated bilirubin, and dysgeusia
Fuzuloparib	Recurrent platinum-sensitive, fallopian tube cancer, or primary peritoneal cancer	150 mg	Nausea, fatigue, asthenia, vomiting, reduced white blood cell count, hemoglobin, platelet count, neutrophil count; and anemia
Pamiparib	Recurrent and advanced ovarian cancer, fallopian tube cancer, and primary peritoneal cancer	60 mg	Nausea, vomiting, fatigue, loss of appetite, diarrhea, abdominal pain, anemia, leukopenia, neutropenia, lymphopenia, thrombocytopenia; elevated AST, ALT, and blood bilirubin levels

**For full details of therapeutic indications, read the information on each PARPi*

2.4.2 Indication and usage

Breast Cancer: This drug is indicated as a single agent for the treatment of adult patients with deleterious or suspected deleterious gBRCAm HER2 -negative locally advanced or metastatic breast cancer [62,65,67].

Prostate cancer: It is also indicated in combination with enzalutamide for the treatment of adult prostate cancer patients with HRR gene-mutated mCRPC [46,65,68].

2.4.3 Dosage and administration

The recommended dose of talazoparib is 1 mg taken orally once daily, with or without food. The 0.25 mg, 0.5 mg, and 0.75 mg capsules are also available for dose reduction. Patients should be treated until the progression of disease or unacceptable toxicity occurs [65,66].

2.4.4 Adverse effects

The most common adverse reactions of talazoparib as a single agent are reduced hemoglobin, neutrophils, lymphocytes, and platelets, elevated glucose, AST, ALT, alkaline phosphatase, fatigue, nausea, headache, vomiting, alopecia, diarrhea, and decreased calcium and decreased appetite. The most common adverse reactions when used in combination with enzalutamide are reduced hemoglobin, neutrophils, lymphocytes,

platelets, calcium, appetite, sodium, phosphate, magnesium, potassium and fatigue, nausea fractures,dizziness, elevated bilirubin, and dysgeusia [Table 1; 64-67].

2.5 Fuzuloparib

Fuzuloparib, also known as SHR3162, AiRuiYi®, or fluzoparib, is a novel, orally available, PARPi and approved in China for the treatment of various cancers. It is the first original PARPi developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd., China, and exhibits higher stability and lower inter-individual variability than other PARPi [69].

2.5.1 Pharmacokinetics

Fuzuloparib is rapidly absorbed with T_{max} is achieved within 2 h and the terminal half-life is 9.14 h after oral administration of 150 mg given twice daily. It is noteworthy that this drug has a higher exposure (Area under the curve; AUC0-24 h) in tumor than that in plasma [70]. A high-fat meal does not affect bioavailability, however, the T_{max} is delayed from 3 h to 6 h. About 74.3–81.6% of administered drug binds to plasma proteins and the apparent volume of distribution is 34.6 L. This dug has a terminal half-life of 9.14 h in patients administered multiple doses of 150 mg twice daily. It is predominantly metabolized by the hepatic enzyme CYP3A4 and eliminated in urine (60%) and feces (40%). Bioavailability is increased with concomitant administration of strong CYP3A4 inhibitors, such as itraconazole and fluconazole while it is decreased with concomitant administration of rifampicin, a CYP3A4 inducing agent [71,72].

2.5.2 Indication and usage

Ovarian cancer: This drug is indicated for the treatment of platinum-sensitive recurrent ovarian cancer, fallopian tube cancer, or primary peritoneal cancer in patients with gBRCA1/2 mutations who had undergone second or later-line chemotherapy [72-74]. It is also indicated as maintenance therapy for platinum-sensitive recurrent ovarian cancer, fallopian tube cancer, or primary peritoneal cancer regardless of BRCA1/2 mutation status [71,73,74].

2.5.3 Dosage and administration

The recommended dosage of fuzuloparib is 150 mg taken orally twice daily [71].

2.5.4 Adverse effects

The most frequent non-hematological adverse reactions of this drug are nausea, asthenia, fatigue, and vomiting. The most frequent hematologic adverse reactions of this drug are reduced white blood cell count, hemoglobin, platelet count, neutrophil count, and anemia. The most common all-grade hematologic toxicity events with fuzuloparib were similar to those of other PARPi [Table 1; 75-77].

2.6 Pamiparib

Pamiparib, also known as PARTRUVIX™, is a selective inhibitor of PARP1 and 2 developed by BeiGene Ltd., China. It is a novel, orally available, PARPi and approved in China for the treatment of various cancers [78,79].

2.6.1 Pharmacokinetics

Pamiparib is rapidly absorbed after oral administration, with a T_{max} of 1 - 2 h. A high-fat food delays absorption and causes a reduction in bioavailability, which is clinically not significant, therefore, the drug can be taken without regard to intake of food. Following administration of the recommended dose, 95.7% drug binds to plasma protein and has an apparent volume of distribution of about 37 L. Concomitant administration with rifampicin, a strong CYP3A inducer, decreased bioavailability while coadministration with itraconazole, a strong CYP3A inhibitor, did not affect its bioavailability [78,79].

2.6.2 Indication and Usage

Ovarian cancer: Pamiparib is indicated for the treatment of recurrent and advanced ovarian cancer, fallopian tube cancer, and primary peritoneal cancer in patients with gBRCA1/2 mutations who have been treated with more than

or equal to 2 previous lines of chemotherapy [78,79]. It is also indicated as maintenance therapy for platinum-sensitive and platinum-resistant recurrent ovarian cancer, fallopian tube cancer, or primary peritoneal cancer regardless of BRCA1/2 mutation status [78-80].

2.6.3 Dosage and administration

The recommended dosage of pamiparib is 60 mg taken orally twice daily until disease progression or unacceptable adverse reactions [79,80].

2.6.4 Adverse effects

The most common adverse reactions of this drug are nausea, vomiting, fatigue, loss of appetite, diarrhea, abdominal pain, anemia, leukopenia, neutropenia, lymphopenia, thrombocytopenia, and elevated AST, ALT, and blood bilirubin levels [Table 1; 78-81].

3. PPAR INHIBITORS RESISTANCE

Notwithstanding the initial successful, improved progression-free survival, and therapeutically potential responses to PARPi, most cancer patients who were administered PARPi often showed a decline in the beneficial effects owing to the development of drug resistance leading to tumor recurrence [82-84]. A growing body of evidence indicates various potential mechanisms of resistance to PARPi which include restoration of HR capacity, stabilization of replication forks, reduced trapping of PARP1, and P-glycoprotein-mediated drug efflux [1,19,83-86]. Furthermore, alterations in cell cycle control, microRNA expression patterns, and various dysregulated signaling pathways have been identified [85-87].

4. STRATEGIES TO OVERCOME PARP INHIBITOR RESISTANCE

Presently, extensive oncological research is progressing to improve understanding of alternative modalities of clinical use of PARPi, optimize efficacy, enhance effectiveness, identify and evaluate novel combinations with other targeted therapies, develop strategies to overcome resistance, and rationalize combination chemotherapy, radiation therapy, or targeted therapies to sensitize tumors [82,83]. Recent research focused on combination therapies as an efficient approach to tackle PARPi resistance [82-84,88,89]. Accumulating evidence shows superior anticancer efficacy of combinational strategies containing PARPi and other kinase or immune checkpoint blockers, such as Ataxia Telangiectasia and Rad3-related (ATR) protein inhibitors that block BRCA1-independent RAD51 recruitment to dsDNA breaks and disrupt fork progression [1,19], and anti-programmed cell death ligand 1(anti-PD-L1) antibodies which show a synergistic effect with PARPi [89-92]. Indeed, blocking cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death 1 (PD-1), and PD-L1 immune checkpoints has emerged as new therapeutic targets in cancer treatment, and these therapies have shown remarkable positive clinical effects.

5. ONGOING CLINICAL TRIALS TO OVERCOME PARP INHIBITOR RESISTANCE

Presently, two phase 2 clinical trials of a combination of olaparib and anti-PD-L1 (durvalumab, tislelizumab, or atezolizumab) for ovarian, breast, and gastric cancers are under progress [28,82,83]. Notably, a well-recognized and focused interest is the combination therapy of PARPi and anti-angiogenic agents in ovarian cancer [83,93]. Various combinations of target-based cancer therapies with PARPi have been undergoing clinical trials including PARPi and PI3K/AKT/mTOR inhibition, PARPi and RAS/RAF/MEK pathway targeting, PARPi and Bromodomain and Extra-Terminal (BET) inhibition, PARPi and c-MET inhibition, PARPi and EGFR/HER2 targeting, PARPi and ATR inhibitors, PARPi and WEE-like kinase 1 inhibitors, PARPi and CDK4/6 inhibitors, and PARPi with other novel DNA damage response (DDR) targets, such as DNA polymerase theta (POLθ or POLQ) inhibitors and ubiquitin-specific protease 1 (USP1) inhibitors [83,84,89,93].

6. CONCLUSIONS

Understanding the molecular pathogenesis of cancer, the genetic concept of synthetic lethality, identification of druggable targets, in particular, PARP1/2, and maneuver of the clinical development of PARPi as the first synthetic lethal targeted therapy in various cancers is a milestone in modern oncology. Recently, six PARPi have been approved, namely olaparib, rucaparib, niraparib, talazoparib, fuzuloparib, and pamiparib, and have the advantage of a superior potency as monotherapy and in combination with other anticancer agents against various cancers. Indeed, PARPi are undergoing investigation to explore their therapeutic potential in other

cancers. Attempts to understand the alternate mechanism of action of sensitivity and resistance of PARPi in cancers and other diseases have been in progress. Importantly, various strategies for PARPi use in combination therapies to overcome resistance and improve sensitivity along with identification and understanding of potential biomarkers are critical in delineating beneficial effects as well as updating oncological clinical practice guidelines.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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