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Original Research

Poly (ADP-ribose) polymerase (PARP) inhibitors as chemosensitizing compounds for the treatment of drug resistant cancers

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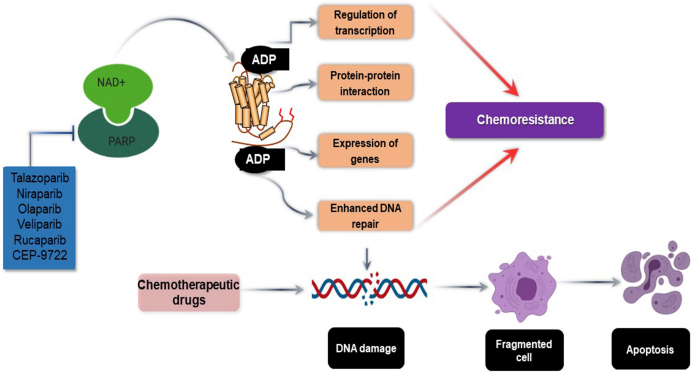

Poly (ADP-ribose) polymerase (PARP) proteins mediate various cellular processes such as DNA repair, regulation of transcription, protein-protein interaction, expression of inflammatory genes and programmed cell death. PARP proteins have a key role in DNA repair and recent findings have established the role of PARP inhibitors as potent chemotherapeutic drugs. Among the 18 members, PARP1 and PARP2 have been identified as the main targets for the development of pharmacological inhibitors to enhance the cytotoxic efficacy of established anticancer drugs. Furthermore, certain PARP1 and PARP2 inhibitors are being used in combination with other drugs for the treatment of various types of cancer. In different drug resistant cancer cell types, PARP inhibitors have been identified as compounds that reverse the resistance to topoisomerase inhibitors, DNA alkylating and methylating drugs by enhancing the DNA damage induced by these agents. In BRCA mutant cells, with abnormal homologous recombination (HR) repair mechanism, BER (Base Excision Repair Pathway) is responsible for survival of the cells. PARP enzymes play a major role in BER and PARP inhibitors effectively target BRCA mutant cells sparing normal cells via the concept of synthetic lethality, producing minimal toxicity to PARP inhibitors also have a significant role in treating pancreatic adenocarcinoma and castration-resistant prostate cancer. The aim of the current paper is to provide a review on PARP inhibitors and their application in the treatment of various cancer cells which are resistant to standard chemotherapeutic drugs.

Keywords

Cancer; chemotherapy; drug resistance; PARP inhibitors; DNA repair; sensitizing agents; overcoming chemoresistance

1. Introduction

Cancer is the abnormal growth of cells due to a dysregulation of cell proliferation [1, 2, 3]. Malignant cells from the primary tumor readily undergo metastasis and invade other tissues and distant organs [4, 5, 6, 7]. The tumor cell microenvironment has a significant impact on the progression and metastasis of human cancer cells [8, 9, 10]. Numerous studies indicate that the abnormal growth and proliferation of cancer cells results from gene mutations, genetic disorders, angiogenesis, tissue invasion, lack of response to anti-apoptotic signals and evasion from immune response [2, 11]. One of the mainstays for the therapy of several types of cancer is chemotherapy [12, 13, 14]. Chemotherapeutic drugs achieve their cytotoxic activity via distinct inhibitory mechanisms including for example: 1) DNA alkylation [15]; 2) Inhibition of DNA replication [16, 17]; 3) Blocking the response to growth and proliferation signals [18, 19] ; 4) Inhibition of microtubule assembly and disruption of mitosis [20]; 5) Inducing apoptosis [21]; and 6) Augmenting the immune response to tumors [22, 23]. However, it is well established that the efficacy of anticancer drugs can be attenuated or abrogated by the development of multiple mechanisms of drug resistance [24, 25, 26, 27, 28, 29, 30]. Consequently, there is a burning need to develop novel drugs that can overcome drug resistant cancers [31, 32]. One potential class of compounds that may be useful in treating certain types of drug resistant cancers are inhibitors of the enzyme poly (ADP-ribose) polymerase (PARP).

The poly (ADP-ribose) polymerase (PARP) family of enzymes

catalyzes the posttranslational ribosylation of proteins by utilizing NAD^+ as a substrate and thereby target proteins undergo mono- or polyADP ribosylation (PARylation) [33, 34]. The ADP-ribose moiety is negatively charged and after addition to the target proteins, it produces structural and functional changes [35, 36, 37]. The PARP enzyme was first characterized in 1963 [38] and currently 18 distinct protein members have been identified in this family [34, 39, 40]. PARP is a multidomain enzyme [41, 42, 43]. The C terminus of PARP contains the catalytic site and is highly conserved, whereas the N terminus has a variable and regulatory motif, a ubiquitin binding site and zinc fingers [44, 45]. Numerous studies indicate that PARP plays a major role in mediating cellular processes such as DNA repair, regulation of transcription, protein-protein interaction, expression of inflammatory genes and programmed cell death [46, 47, 48]. PARP is a *bona fide* target for the advancement of drugs for the treatment of breast, ovarian and prostate cancer [40, 49, 50]. PARP1 and PARP2 are known as polyADP ribose transferases because they catalyze the transfer of ADP-ribosyl to target proteins [51, 52]. PARP enzymes have a very short half-life (i.e., $<$ 1 minute) [53, 54] and they are biotransformed and inactivated by the enzymes polyglycohydrolase, ADP-ribosyl ligase and ADP-ribosyl-acceptor hydrolase-3 [46, 55]. PARPs are primarily active in the nucleus, and typically have low activity in the cytoplasm [56, 57].

The current PARP inhibitors target PARP1 and PARP2 and there are at least 42 compounds known to inhibit these enzymes, 4 inhibitors of which (i.e., olaparib, rucaparib, niraparib and talazoparib) are approved by the United States Food and Drug Administration (FDA) for the treatment of various human malignancies [58, 59, 60, 61]. PARP1 plays a vital role in repairing DNA single strand breaks (SSB), which are caused by oxidative stress through the base excision repair/SSB repair (BER/SSBR) pathway [62]. PARP1 has three domains: a DNA binding domain, a catalytic domain and an auto-modification domain [35, 63, 64]. The DNA binding domain interacts with damaged DNA segments and has three zinc finger motifs that confines PARP1 to the nucleus [65, 66]. Zinc finger 2 has a high affinity for DNA fragments, whereas zinc fingers 1 and 3 mediate DNA-dependent PARP1 activation [67, 68]. The automodification domain dissociates the protein from the DNA substrate [42, 69] and the catalytic domain facilitates the binding of NAD^+, thereby catalyzing ADP ribosylation of target proteins [35, 48]. PARP 1 and PARP2 are structurally similar in many aspects except that PARP 2 does not have zinc fingers and has a short N-terminal DNA binding domain [70]. PARP 2 was first shown to be in the cells of PARP1 knockout mice that generated an ADP-ribose polymer from NAD^+ in response to DNA damage [71]. Since the discovery of PARP1 and PARP2, a family of 17 proteins has been identified that are similar to the catalytic domain of PARP1, but only PARP3, Vault PARP as well as PARP 5a and 5b (also known as Tankyrases 1 and 2, respectively) have been shown to have ADP-ribose polymerization activity [72, 73].

As a result of their role in cellular processes that are involved in cancer, specific PARP enzymes have been investigated as targets for novel anticancer drugs [40, 74, 75]. Dysregulation of cell proliferation, DNA repair and cell cycle induce tumorigenesis and are regulated by the PARP family of enzymes [52, 76]. For example, if single stranded DNA breaks occur, PARP 1 and PARP 2 are promptly activated and rapidly bind to the DNA damage site, where they activate the DNA repair process [44, 77]. The inhibition of PARP by small molecules has been shown to increase the efficacy of chemotherapy and radiotherapy in certain types of cancers [78, 79, 80]. Indeed, PARP inhibitors increase the efficacy of cytotoxic drugs including: 1) Compounds that methylate DNA such as temolozolomide, 2) topoisomerase 1 inhibitors including irinotecan and topotecan, as well as 3) ionizing radiotherapy [81, 82, 83]. Numerous studies have reported that defective DNA repair pathways can enhance tumorigenesis [84, 85, 86]. Recent studies have shown that specific types of tumor cells with a defective homologous recombination (HR) repair pathway are very sensitive to certain PARP inhibitors [87, 88]. For example, BRCA1/2-deficient cancer cells are more sensitive to PARP inhibition, which causes decreased base excision repair (BER), leading to persistent DNA damage, a concept called synthetic lethality (Fig. 1). As under normal conditions, DNA damage would be repaired via HR [89, 90, 91]. However, HR defects are not limited to BRCA-deficient tumors and other types of cancer may also be enriched by HR defects which make the PARP inhibitors suitable for treating other classes of cancers. For example, if cancer cells have somatic mutations or epigenetic silencing in any part of the HR pathway, PARP inhibitors could induce the death of these cells [91]. In addition, the activity in any other part of the HR pathway could also been monitored by other proteins [92]. Mutations in the gene that encodes for the tumor suppressor protein phosphatase and tensin homolog (PTEN) have been shown to enhance the likelihood of cancer [93]. Furthermore, PTEN deficiency can decrease HR and was successfully targeted by the PARP inhibitor olaparib [94]. There are anticancer drugs whose efficacy is due to DNA damage, which causes the cancer cell death [95]. In several of the completed preclinical studies, PARP inhibition enhance DNA damage induced by cisplatin and gemcitabine [96, 97, 98]. The efficacy of such drugs can be attenuated or abolished by activation of the cellular DNA repair pathways [99]. Furthermore, these pathways can be upregulated in tumors, resulting in drug resistance [100]. PARP1 plays a role in the removal and repair of DNA single strand breaks caused by ionizing radiation, methylating and alkylating agents, topoisomerase I inhibitors and other cytotoxic drugs that damage DNA such as bleomycin [81, 83, 96]. Therefore, drugs that inhibit PARP1 can enhance the antitumor activity of chemotherapeutic drugs which inflict DNA damage [96]. Clinical studies indicate that the combination of the PARP inhibitor iniparib and CEP-9722, and the platinum drugs, carboplatin and cisplatin, respectively, significantly improves the prognosis in breast cancer patients, indicating that PARP inhibitors enhance the efficacy of drugs that produce DNA damage [80, 96, 101].

Finally, PARP inhibitors can also be used to treat sporadic, high-grade serous ovarian cancer (HGS-OC) and additional types of cancers which also have DNA repair deficiencies, including endometrial, pancreatic, and prostate and cancer [78, 102, 103, 104]. In this review, we outline the different PARP inhibitors and their mechanisms in cancer treatment (Table 1); their structures are depicted in Fig. 2.

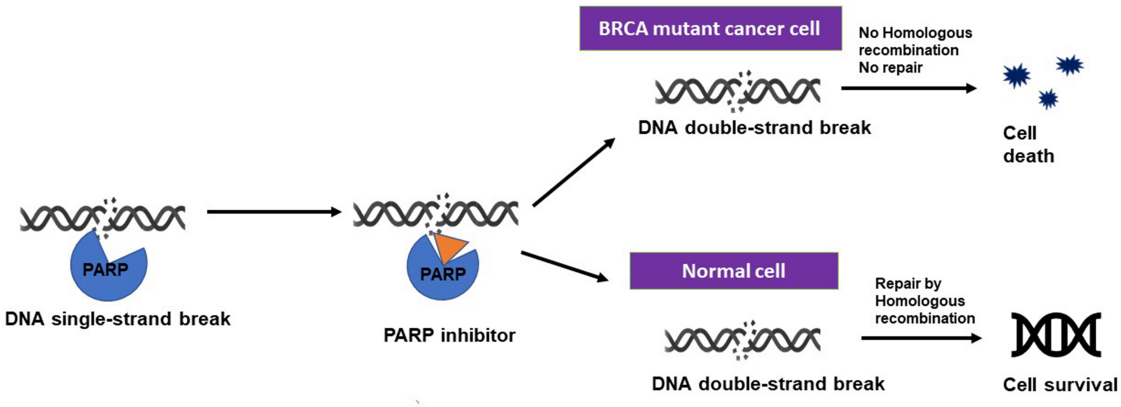

Figure 1. Synthetic lethality of Poly (ADP-ribose) polymerase (PARP) inhibitors. PARP enzymes play a vital role in DNA damage repair. DNA damage can be repaired via homologous repair (HR) mechanisms in normal cells. BRCA mutant tumors are inherently defective in HR repair. PARP inhibitors cause DNA damage which cannot be repaired by HR mechanisms, thereby cause the selective apoptosis of these cells.

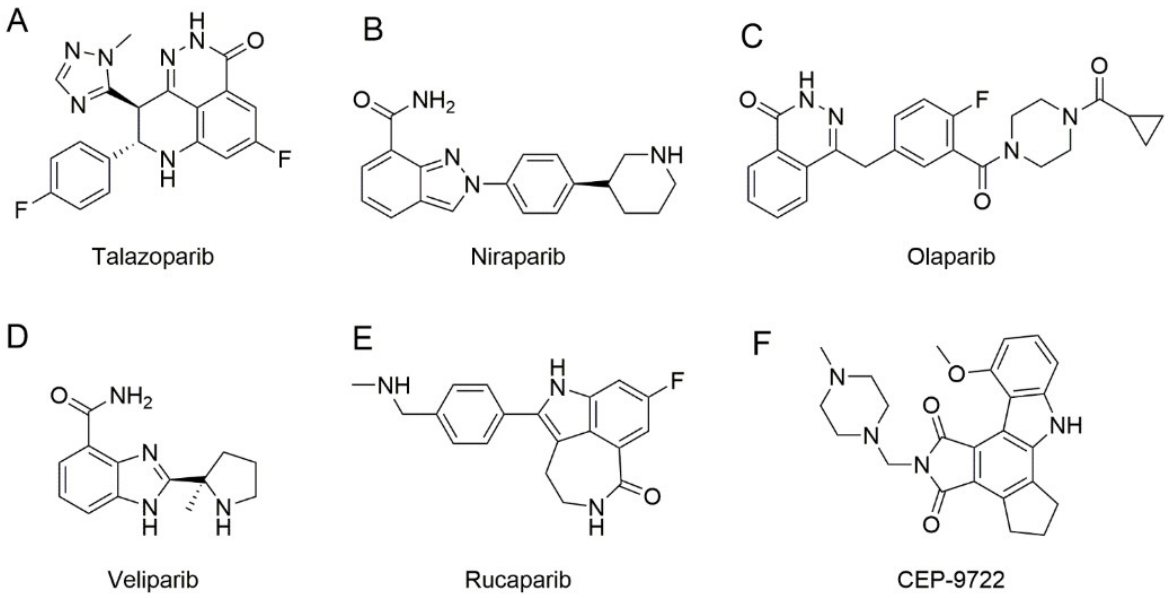

Figure 2. The structures of PARP inhibitors that sensitize cancer cells to conventional chemotherapeutic drugs.

2. PARP inhibitors-Detailed description

2.1 Talazoparib

Talazoparib's inhibitory activity depends on its unique binding interactions with the NAD^+ site as well as the active enantiomer (trans) configuration, which is responsible for π-stacking and hydrogen-bonding interactions mediated by water between the fluorophenyl and 1,2,4-triazole groups of talazoparib with Tyr889 and Tyr896 residues of PARP1 [105]. Talazoparib (5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1H-1,2,4-triazol-5-yl)-2,7,8,9-tetrahydro-3H-pyrido[4,3,2-de] phthalazine-3-one) was recently approved by the FDA for the treatment of patients with deleterious or suspected deleterious inherited BRCA germline mutations [106] and human epidermal growth factor receptor-2 (HER-2) negative breast cancer [107, 108]. Talazoparib irreversibly inhibits PARP1 and PARP2 which regulate cell cycle progression, initiation of the DNA damage response, and apoptosis [105, 109, 110]. Talazoparib traps PARP on single-stranded DNA breaks, producing cytotoxicity [111]. PARP inhibition by talazoparib causes lethality in cancer cells with BRCA1/2 mutations due to their deficiency in HR-dependent DNA repair and the accumulation of irreversible DNA damage which induces cell death [112, 113, 114]. Furthermore, talazoparib has greater PARP inhibitory efficacy than olaparib [115], as it inhibits double stranded DNA break repair, producing alternative non-homologous end joining instead of HR [116], leading to cytotoxicity. Preclinical studies in both human and animal tumor models indicated that talazoparib had a pharmacokinetic profile suitable for progression into clinical trials [117, 118]. The oral bioavailability of talazoparib in rats was more than 40% and based on this, it was predicted that talazoparib could be administered once a day [118]. Pharmacokinetic data have been evaluated from phase I, phase II and phase III studies in cancer patients, over a dose range of 0.025-2 mg/day [119]. Talazoparib undergoes cysteine conjugation to form monodesfluoro-talazoparib, dehydrogenation, monooxidation and glu-

Table 1. The different PARP inhibitors and their mechanisms in cancer treatment

Compound	Target of interaction	FDA status	Dose	Route	Adverse effects
Talazoparib	Inhibits PARP 1 and 2	Approved for advanced breast cancer	1 mg, once a day	oral	Anemia, neutropenia and thrombocytopenia.
Niraparib	Inhibits PARP 1 and 2	Approved for ovarian and fallopian cancer	300 mg, once a day	oral	Thrombocytopenia, fatigue and anemia.
Olaparib	Inhibits PARP 1 and 2 and 3	Approved for advanced ovarian cancer	300 mg, twice a day	oral	Vomiting, anemia and diarrhea
Veliparib	Inhibits PARP 1 and 2	Phase III for breast and ovarian cancer	120 mg, twice a day	oral	Grade 2 nausea, vomiting, fatigue, and anemia
Rucaparib	Inhibits PARP 1,2 and 3	Approved for advanced ovarian cancer	600 mg, twice a day	oral	Anemia, nausea, vomiting, thrombocytopenia, shortness of breath.
CEP-9722	Inhibits PARP 1 and 2	Phase I for urothelial cancer	150-1000 mg, once a day	oral	Neutropenia, leukopenia, and anemia

curonidation and is excreted primarily in the urine in its parent form [106, 119]. The mean plasma half-life is approximately 90 hr in cancer patients [106]. A dose of 1 mg/day is recommended in patients to reduce the occurrence of adverse effects, but the dose must be decreased in patients with moderate and severe renal impairment [106, 119]. *In vitro*, talazoparib does not significantly inhibit or induce hepatic CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 [108].

Talazoparib has been considered as monotherapy for neoadjuvant patients [120]. A study with 13 breast cancer patients with a germline BRCA mutation that received talazoparib as monotherapy for 2 months before neoadjuvant therapy (anthracycline and taxane based chemotherapy ±carboplatin) and surgery displayed a significant decrease (approximately 88%) in tumor volume [107]. Another study (NCT02282345) with 20 advanced breast cancer patients with a germline BRCA mutation indicated that administration of talazoparib 6 months prior to surgery produced a complete pathologic response [113]. The combinations of talazoparib with other anticancer drugs has yielded significant therapeutic efficacy. Talazoparib, when used in combination with temozolomide, produced a 59-, 35- and 1500-fold greater cytotoxic efficacy in Lovo cells (colon cancer cells) compared to monotherapy treatment with the PARP inhibitors olaparib, rucaparib and veliparib, respectively [105]. In BRCA-deficient breast cancer patients, combination therapy of talazoparib, with cisplatin or temozolomide, produced significant positive response rates up to 73% [121]. Previously, talazoparib was reported to be more efficacious than olaparib or talazoparib as a radiosensitizer in glioblastoma stem cells *in vitro* [122]. Furthermore, talazoparib (12.5 nM), compared to veliparib and olaparib, displayed greater efficacy in sensitizing the olaparib-resistant breast cancer cell line, CAL51 by targeting genes involved in Homologous repair/Double stranded DNA break repair pathways such as BRCA1/2(breast cancer resistance protein), SHFM1 (split hand/foot malformation gene), PKNB (protein kinase B gene), PALB2 (Partner and localizer of BRCA2 gene), ATM (Ataxia-Telangiesctasia gene), ATR(Ataxia-Telangiesctasia and Rad3 related gene), CHEK1 (Checkpoint kinase 1 gene), FANCM (Fanconi anemia complementation group M), FANCA (Fanconi anemia complementation group A) etc. [118]. The common untoward toxicity produced by talazoparib was anemia, neutropenia and thrombocytopenia, which can be minimized by a dose reduction [113, 114].

2.2 Niraparib

Niraparib (2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-2H-indazole -7-carboxamide) was approved by U.S. FDA on March 2017 and EMA for the maintenance treatment of recurrent epithelial ovarian and fallopian tube or primary peritoneal cancer patients [123]. Niraparib not only blocks the DNA repair mechanism by inhibiting the BER pathway, but also traps PARP-1 and PARP-2 at the sites of DNA damage, producing cytotoxicity [124, 125]. Niraparib has displayed higher PARP binding affinities as it mimics the structure of the amide group of nicotinamide binding domain and is responsible for three important hydrogen bonds to the hydroxyl group of Ser904 and the amide backbone of Gly863, along with the pyridyl ring which is responsible for $\pi - \pi$ interactions with Tyr907 [125].

Pre-clinical data indicate that niraparib (1 μM) augments the effect of radiation therapy in tumor cell-based and murine xenograft models, independent of p53 status [126]. In human derived lung and breast cancer xenograft models, including a triple negative breast cancer xenograft, niraparib (50 mg/kg, orally) sensitized the xenografts to radiation therapy in a p53-independent manner [127].

A phase I dose escalation trial has shown that niraparib does not produce significant adverse effects up to a maximum dose of 300 mg/day in patients harboring a BRCA mutation and in patients with sporadic cancers [128]. Niraparib is primarily biotransformed by hepatic carboxylesterase which produces inactive drug metabolites that are glucuronidated and excreted into the urine and feces [129, 130]. Similar to talazoparib, naraparib does not significantly interact with cytochrome P450 hepatic enzymes [131]. Niraparib has a mean half-life of 36 h following multiple daily doses, with an oral bioavailability of 73% [60]. In humans, at steady state levels, niraparib has a higher volume of distribution (approximately 1500 L) compared to olaparib (approximately 158L) [132, 133]. Niraparib crosses the blood-brain barrier (BBB) and its levels in the brain are greater than olaparib, as it is expelled to a lower extent than olaparib by the ABC transporters BCRP and P-gp in the BBB [134].

The results of the PRIMA trial indicate that niraparib can be a first line treatment for longer periods of PFS (progression - free

survival) in patients diagnosed with advanced recurrent ovarian cancer [135]. Niraparib, when used in combination with irinotecan, potentiated the cytotoxic effects of irinotecan in microsatellite instable (MSI) and stable (MSS) colorectal cancer models *in vitro* [136]. Niraparib, when combined with cyclophosphamide, displayed a significant efficacy in treating triple negative breast cancer patient-derived xenograft human models [137]. Niraparib is efficacious in inhibiting the growth of tumors in patient-derived xenograft models, regardless of the BRCA or homologous recombination deficiency (HRD) status [132, 138]. During the phase III NOVA trial, adverse effects commonly reported for niraparib were thrombocytopenia, fatigue and anemia, which can be minimized by adjusting the dose [139]. The ongoing phase I, II and III clinical trials (NCT02854436, NCT03748641, NCT03431350, respectively) will determine the efficacy of niraparib alone or in combination with drugs like abiraterone, prednisolone and JNJ-637283 (an immune checkpoint inhibitor), for the treatment of prostate cancer [50].

2.3 Olaparib

Olaparib(4-(3-{[4-(Cyclopropylcarbonyl)-1-piperazinyl]carbonyl}-4-fluorobenzyl)-1(2H)-phthalazinone) was the first drug from the family of PARP inhibitors that was approved by the FDA in 2014 for the treatment of ovarian cancer [140]. It inhibits PARP1 and PARP 2 which results in double-stranded DNA breaks that produces apoptosis in cancer cells [140, 141]. Olaparib contains oxygen atoms which forms hydrogen bonds with backbone atoms in the catalytic domain of Arginine and also water mediated hydrogen bonds with aspartic acid and Van der Waals Force interaction with aliphatic side chain of glutamic acid in the regulatory domain [142]. Olaparib was approved both in Europe and USA as maintainence treatment in platinum-sensitive ovarian cancer patients, independent of their BRCA1/2 mutation status [143].

Olaparib can be administered orally at daily doses amounting 200-600 mg, depending on the renal function of the patient [141]. Its peak plasma concentration occurs 1-3 hours after administration [144] and it has a terminal elimination half-life of 11.9 h following a 400 mg dose [141]. Olaparib has an apparent volume of distribution 167 L and is primarily metabolized in the liver by dehydrogenation and oxidation, and it undergoes glucuronide and sulfide conjugation [144]. Olaparib is primarily excreted unchanged in the urine and consequently, olaparib's renal clearance is decreased in patients with diminished renal function [141]. Furthermore, in patients with mild (GFR = 51-80 mL/min) to moderate renal impairment (GFR = 31-50 ml/min), there was a decrease in the volume of distribution and terminal half-life compared to patients with normal renal function [145, 146]. The most common adverse events of any grade reported following treatment with olaparib were nausea, fatigue, vomiting, anemia and diarrhea, although severe grade 3 or 4 anemias have been reported in some patients and this could be managed by a dose reduction [147, 148]. Olaparib increases the efficacy of the platinum drugs cisplatin and carboplatin, in both *in vitro* and *in vivo* models of BRCA-deficient mouse mammary cancers [149]. Olaparib also increased the efficacy of cisplatin in BRCA-deficient mouse mammary cell lines [150]. When used as a monotherapy, olaparib has been shown to produce antitumor efficacy in BRCA-deficient mouse models [151]. Data from a Phase I study (NCT00494442)has shown that olaparib alone has antitumor efficacy in pretreated BRCA1 and BRCA2-deficient patients with recurrent ovarian cancer [152]. Phase III trials with olaparib have shown a significant increase in the quality of life and a longer PFS in: 1) ovarian cancer patients with a germline BRCA1/2 mutation who were previously treated with platinum chemotherapy [153] and 2) patients with platinum-sensitive relapsed ovarian cancer [143, 148].

Olaparib has been reported to have efficacy in the treatment of castration-resistant prostate cancer (CRPC) based on the results of the TOPARP-A trial where 16 patients were previously treated with abiraterone, enzalutamide or cabazitaxel, followed by olaparib at 400 mg twice a day until the primary response rate (decrease in PSA) was observed. The results indicated that there is a significant decrease in PSA levels and decreased circulating tumor cell counts which reflect its antitumor activity [154]. Another trial namely POLO, indicated that olaparib maintenance treatment of 300 mg twice a day for 4 to 8 weeks, produced a substantial (PFS) in metastatic pancreatic cancer patients with BRCA mutations who had not benefited from platinum-based chemotherapy [155]. A phase I/II trial that was designed to evaluate the effectiveness of olaparib 100-200 mg twice a day for a 21-day cycle in combination with temozolomide in patients who were formerly treated for small cell lung cancer. There was a significant increase in PFS [156, 157]. The data form the phase III trial, OlympiAD, reported that olaparib monotherapy of 300 mg twice daily for 21 days (dose and length of treatment) in patients with HER-2 negative metastatic breast cancer and a BRCA mutation had a significant longer PFS when compared to patients treated with capecitabine, eribulin, or vinorelbine in 21-day cycles [158].

2.4 Veliparib

Veliparib (ABT-888) has high potency in inhibiting PARP1/2, with Ki values of 5.2 (PARP1) and 2.9 (PARP 2) nM, as determined by *in vitro* fluorescence assays [102]. The amide group of veliparib binds with PARP active site, and intermolecular hydrogen bonds are formed between amide bond and Gly-863/Ser-904. Moreover, veliparib also forms a π-π stacking with Tyr-907 [159]. Veliparib, similar to other PARP inhibitors,: inhibits PARP1 and PARP2, which disrupts the BER mechanism and consequently induces DNA damage, resulting in induction of cellular apoptosis [160].

Veliparib alone has been reported to have limited *in vitro* efficacy in a panel of lung cancer cells [161]. However, in a xenograft model of SCLC (H146 and H128 cells in the flank region of 6-week-old athymic nu/nu mice), the administration of 25 mg/kg i.p. of veliparib and 2.5 mg/kg i.p. of cisplatin for 4 weeks, significantly decreased tumor size compared to animals treated with cisplatin or etoposide alone [160]. Also, *in vitro*, veliparib (10 µM for 24 or 72 h) significantly increased DNA-damage signaling (i.e., pKAP1S824, pChk1S345 and pChk2T68) in the glioblastoma multiforme cell lines T98G, U251 and U251TMZ [162].

Currently, 10 clinical studies related to veliparib have been approved by the FDA, including 6 phase III clinical trials. In April 2014, the FDA approved a phase III trial of veliparib for squamous NSCLC; however, the outcome missed the primary expectation, which was a significant increase in overall survival, PFS and objective response rate. Veliparib was also approved for a phase III

clinical trial in HER2$^-$ metastatic or BRCA$^+$ breast cancer in August 2014, although there has been no patient recruitment. Besides the 6 phase III clinical trials mentioned above, multiple ongoing or completed phase I or II clinical trials have been approved by the FDA. A phase I trial of veliparib and metronomic cyclophosphamide [163], which focused on various types of refractory cancers (i.e., ovarian, carcinoid, breast, colon, pancreas, urothelial, melanoma, sarcoma, endometrial, lymphoma and unknown type), was approved. Thirty-five patients were given 60 mg of veliparib (orally, once daily for 21 days) and 50 mg of cyclophosphamide (orally, once daily for 21 days) [163]. The results indicated that 6 patients had their disease stabilized for at least 6 cycles and 7 patients had partial responses. In addition, in 7 patients, there was a decrease in peripheral blood mononuclear cells (PBMCs) and an increase in phosphorylated histone (VH2AX) levels, which is a biological marker of DNA damage in circulating tumor cells. In 2015, a phase II study was performed to confirm the efficacy of combining veliparib and cyclophosphamide in patients with ovarian cancer. After oral administration (50 mg/day cyclophosphamide and 60 mg/day veliparib) in a 21-day cycle, veliparib failed to improve the response rate [164].

2.5 Rucaparib

Rucaparib (AG014699, RubracaTM) is a small molecule PARP1, PARP2 and PARP-3 inhibitor [165]. It forms hydrogen bond interaction with Gly-863 located in the binding site of PARP-1. TYR889, TYR896 and TYR907 are likely to participate in forming π-π interaction with the indole core [166]. The mechanism of action of rucaparib has been previously characterized by Robillard et al [167]. Rucaparib selectively inhibited PARP1, PARP2 and PARP3, with IC_{50} values of 0.8, 0.5 and 28 nM, respectively. Also, in the UWB1.289 (ovarian cancer) cell line, rucaparib decreased poly-ADP ribosylation in a concentration-dependent manner, with an IC_{50} value of 2.8 nM, and increased DNA damage and apoptosis [167]. Oral rucaparib was approved by the FDA for the treatment of advanced ovarian cancer with deleterious BRCA mutations [168]. The FDA has approved 51 clinical trials with rucaparib for multiple cancer types including ovarian, prostate, urothelial, cervical, lung and breast (clinicaltrials.gov). Additionally in a phase II trial of rucaparib in relapsed high-grade ovarian cancer patients with platinum-sensitive tumors, the risk of progression during treatment with rucaparib (oral, 600 mg, twice daily for a 28-day cycle) was significantly reduced in BRCA-mutant and BRCA-wild-type groups [169]. Subsequently, a phase III clinical trial with rucaparib in recurrent ovarian carcinoma after treatment with platinum therapy indicated that the patients treated with rucaparib had a significantly greater median progression-free survival time in patients with a BRCA-mutant carcinoma (5.4 months in placebo group versus 16.6 months in the rucaparib group) [170]. The efficacy of rucaparib has also been evaluated in patients with metastatic melanoma who were receiving temozolomide [59]. The results showed that the administration of temozolomide (150-200 mg/m^2/day) and a PARP inhibitory dose (12 mg/m^2/day) of rucaparib increased PFS compared to historical controls [171]. At the end of 2019, two new clinical studies were approved by the FDA: a phase I study involving the treatment of metastatic castration resistant prostate cancer with rucaparib, enzalutamide and abiraterone (Dec, 2019) and a phase II study of rucaparib in patients with solid tumors, prostate, breast, ovarian, fallopian tube and peritoneal with a mutation in one or more genes, including breast cancer gene (BRCA1/2), partner and localizer of BRCA2 gene (PALB2), DNA double strand repair gene (RAD51B/C/D), BRCA1-associated ring domain gene (BARD1), BRCA1-interacting protein gene (BRIP1), Fanconi anaemia complementation group gene (FANCA), nibrin gene (NBN) with deleterious mutations in homologous recombination repair (HRR) genes (clinicaltrial.gov). These two studies are newly approved and have not started recruitment yet.

2.6 CEP-9722

CEP-9722 (11-methoxy-2-((4-methylpiperazin-1-yl)methyl)-4,5,6,7-tetrahydro-1H-cyclopenta[a]pyrrolo[3,4-c]carbazole-1,3(2H)-dione), a pro-drug which is biotransformed to another compound, CEP-8983 (11-methoxy-4,5,6,7-tetrahydro-1H-cyclopenta[a]pyrrolo[3,4-c]carbazole-1,3(2H)-dione) and it is an inhibitor of PARP1 and PARP2 [172]. CEP-9722 is rapidly metabolized to CEP-8983 in less than 5 minutes [172]. The *in vitro* study shown that CEP-9722 (0.1-10 μM) increased the number of DNA single-stranded breaks, inducing cell instable and apoptosis [172]. As this compound is a new drug in early stages of development, the published studies focus primarily on clinical efficacy and have not focused on investigation of the interaction of CEP-9722 with its PARP target [172]. Although there have been several pre-clinical studies and three clinical trial studies performed to evaluate the clinical application of CEP-9722, it remains to be approved by the U.S. FDA. *In vitro*, CEP-8983 increased the efficacy of certain anticancer drugs in chemoresistant tumors by prolonging the duration of DNA damage and increasing apoptosis [173, 174, 175]. However, the *in vitro* incubation of CEP-9722 with temozolomide or topotecan, respectively, did not increase chemotherapy-related myelotoxicity based on results from a granulocyte-macrophage colony-forming unit assay [172]. In addition, CEP-9722 alone displayed anti-tumor efficacy in human colon carcinoma HT29 cell xenografts in nude mice and in a chemoresistant rat glioblastoma RG2 cell xenografts in rats and CEP-9722 decreased the accumulation of PARP in glioma xenografts in a dose- and time-dependent manner [172].

Jian et al. (2014) investigated the effect of CEP-9722 and CEP-8983 on urothelial carcinoma (UC). CEP-9722, compared to CEP-8983 or cisplatin alone, produced an increase in DNA damage in the human UC cell lines RT4 and 5637 cells. CEP-9722, at 200 mg/kg administered by oral gavage, once daily for 5 days a week for 4 weeks via oral gavage, significantly decreased tumor growth in RT4 xenografts compared to animals treated with vehicle alone. Immunohistochemistry data indicated that cleaved caspase-3 levels were significantly increased, whereas there was a decrease in the expression of CD31, the platelet cell adhesion molecule-1 that is a biomarker of angiogenesis. The evaluation of biomarkers indicative of PARP inhibition in UC is sound because the efficacy of CEP-9722 is inversely proportional to the HRR reaction involved in DNA damage repair [176]. A phase I trial with temozolomide supported the hypothesis that CEP-9722 may cause less myelosuppression compared to all other oral PARP inhibitors [174]. In this study, 26 patients with solid tumors were treated orally with increasing doses of CEP-9722 from 150- 1000 mg/day for 14 days, and then treated for 28-days with 1000 mg/day of CEP-9722 and

150 mg/m^2/day temozolomide for all the treatment period. Although there were significant interpatient and intrapatient variation, the plasma levels of CEP-8983, which is the active form of CEP-9722, was used to assess the relative plasma concentration of CEP-9722. It is worth noting that the plasma concentrations of CEP-8983 were lower in patients taking drugs that may increase gastric pH as well as in cigarette smokers, which may result from the poor solubility of CEP-8983 in non-acidic environments and an increased metabolism of CEP-8983 due to an increased expression of CYP1A2, respectively [174]. Subsequently, the safety, efficacy and pharmacokinetic profile of CEP-9722 combined with oral temozolomide was evaluated in patients with advanced solid tumors such as breast, colorectal, and ovarian cancers. The results revealed one case of a partial response, four cases with a stable disease and 17 cases showed disease progression and CEP-9722 and temozolomide treatment was stopped at cycle 12 due to concerns about the cumulative toxicity of temozolomide [174]. As previously reported, CEP-9722 produced a lower magnitude of myelosuppression compared to other PARP inhibitors.

Awada et al., (2016) conducted a study to determine the maximum tolerable dose of CEP-9722 when combined with either gemcitabine or cisplatin in patients with advanced solid tumors. Thirty-two patients were given 75 mg/m^2 of cisplatin and 1,250 mg/m^2 of gemcitabine on the first day of the study and the eighth day of the 21-day treatment cycle. However, only 18 patients who completed the first chemotherapy cycle with cisplatin and gemcitabine were treated orally with 150, 200, 300, or 400 mg of CEP-9722 twice daily from the second day to the seventh day and dose-limiting toxicities were evaluated. Patients were allowed to proceed with treatment until the disease progressed or the adverse toxicity was determined to be unacceptable. The median treatment range for CEP-9722 was five (1-12) cycles and no patients had dose-limiting toxicity after CEP-9722; however, 33% of the patients stopped treatment due to adverse effects. At the end of the study, there was one patient with a complete remission, three patients with partial remission and eleven patients displayed a stable disease. Prior to the determination of the maximum tolerable dose, the study was discontinued due to significant changes in the exposure to CEP-8983 in all cohorts and toxicity with myelosuppression [96].

3. Acquired resistance to PARP inhibitors

There are a number of mechanisms that can produce resistance to PARP inhibitors. Mutations in BRCA1 and BRCA2 (tumor suppressor genes), predispose to various human cancers including, breast, ovarian, pancreatic and prostate cancer [177, 178]. The HR pathway is important for the repair of double-stranded DNA breaks [179, 180] and BRCA is a main factor in double-stranded DNA break repair via the HR mechanism [181, 182]. Inhibition of the HR pathway can induce apoptosis [183] and the efficacy of PARP inhibitors is greater in HR-deficient than in non-HR-deficient cancer cells [184]. In addition, cancer cells that lack the BRCA genes are susceptible to PARP inhibitors and the restoration of BRCA genes causes resistance to PARP inhibitors [84, 85].

Overexpression of the ABC transporter, ABCB1, in a P-gp-proficient mouse model has been reported to cause a lower survival rate compared to P-gp-deficient mice which were given olaparib for 28 days [185]. This is due to due to the efflux function of the ABC transporter, ABCB1/P-gp, which extrudes PARP inhibitors from cancer cells, leading to resistance to PARP inhibitors including rucaparib or olaparib [185]. ABCB1-mediated resistance has been shown to occur in mice with BRCA1-deficient breast tumors [101]. The marked expression P-gp in A2780 ovarian cancer cells produced a 36-fold increase in the concentration of olaparib required to inhibit growth by 50% and this acquired resistance can be surmounted by ABCB1 inhibitors like verapamil [186]. The loss of the p53-binding protein 1(53BP1) has been reported to produce resistance by restoring BRCA function [187, 188, 189]. The HR pathway is inhibited by 53BP1 and the loss of 53BP1 restores the activity of BRCA- mediated HR and causes resistance to olaparib [185, 190]. Furthermore, loss of 53BP1 produced resistance to olaparib by increasing the expression of P-gp, thereby increasing olaparib efflux, hence attenuating its cytotoxic activity [101]. It has been shown that 53BP1 is not expressed in BRCA1/2 mutated breast cancer cells [191] and the survival rate of patients with BRCA1/2 mutated breast cancer is low due to an increase in resistance to drugs that cause DNA damage, such as cisplatin and mitomycin. It has been postulated that the expression of 53BP1 could be used to ascertain the efficacy of PARP inhibitors upon treatment of BRCA1-deficient tumors [190].

PARylation is a reversible modification of the PARP enzyme and other nuclear proteins and these PAR chains formed facilitate the recruitment of DNA repair enzymes; PAR modifications turn over rapidly due to the activity of poly-(ADP-ribose) glycohydrolase (PARG) [191]. PARG catalyzes the removal of PAR chains from post-translationally modified proteins, releasing poly ADP-ribose [191, 192]. PARG can thus eliminate nuclear PARylation and this could nullify the function of PARP1 [193]. In an HR-deficient mouse model, loss of PARG activity induced resistance to PARP inhibitors by restoring the activity of PARP [193].

The depletion or loss of the PARP1, as well as a decrease in the affinity of PARP1 inhibitors, have been shown to produce resistance to PARP inhibitors such as olaparib [193, 194, 195]. Ovarian cancer cells, as well as tumors from patient-derived xenografts (Makvandi et al., 2018), that do not express PARP1, are resistant to olaparib. There is a positive correlation between PARP inhibitors efficacy and the level of functional PARP 1 levels [196]. Moreover, mouse embryonic stem (ES) cells with PARP 1 mutation are highly resistant (~100-fold) to olaparib than cells with wild type PARP 1 [197].

4. Conclusions

PARP inhibitors are a new class of drugs that improved the outcome in several cancer types. The deficiency in DNA repair mechanisms causes extensive irreversible DNA damage leading to apoptosis and PARP inhibitors have proved to target these mechanisms. This contributes to the use of clinical PARP inhibitors along with DNA damaging agents, thereby restoring cancer cell chemosensitivity to conventional drugs. PARP inhibitors have a great impact in women with ovarian cancers and in either somatic or germline BRCA1/2 mutations, they are used as a maintenance therapy and increase the overall survival rate. The present article focused on FDA approved PARP inhibitors like talazoparib, niraparib, olaparib and rucaparib and other drugs like veliparib and

CEP-9722 which are currently undergoing clinical trials and are under extensive investigation. Because of the low toxicity profiles, they are ideal for the prolonged treatment of cancer. However, tumors can develop mechanisms of resistance to PARP inhibitors, due to occurrence of secondary mutations, increased drug efflux, decrease PARP level and loss of 53BP1 function. A better understanding of these molecular mechanisms of chemoresistance is important to for the selection of the most efficacious drug treatment. Overall, PARP inhibitors have gained a great attention for their activity in HR-deficient tumors and further research can be conducted to expand their clinical utility in various cancers.

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Conflict of interest

The authors declare no potential conflicts of interest.

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