European Journal of Medical and Health Sciences
www.ejmed.org

PARP Inhibitor for Ovarian Cancer Therapy

I Nyoman Bayu Mahendra and William Alexander Setiawan

ABSTRACT

Almost all ovarian cancers are comprised of epithelial ovarian cancer (EOC). Approximately 80% of patients with EOC initially respond to standard cytoreductive therapy and postoperative platinum-based chemotherapy. However, due to drug resistance in high-grade serous ovarian cancer (HGSOC), recurrence is almost inevitable. Recently, the nuclear enzyme poly (ADP ribose) polymerase (PARP) represents a surprisingly new target in EOC therapy. Inhibitors of PARP have demonstrated promising efficacy in the treatment of EOC. Studies on Olaparib, in particular, hastened its approval in the USA and Europe. The main topics of this study are the pre-clinical evidence, ongoing clinical studies, recent advancements in PARP inhibitor technology, and their potential future roles in clinical care for EOC patients.

Keywords: EOC, PARP, Olaparib.

Submitted : August 28, 2022

Published : November 9, 2022

ISSN: 2593-8339

DOI: 10.24018/ejmed.2022.4.6.1477

I. N. Bayu Mahendra*
Obstetrics and Gynecology Department, Sanglah Hospital/ Medical Faculty, Udayana University, Indonesia.
(e-mail: bayu.mahendra.nyoman@gmail.com)

W. A. Setiawan
Obstetrics and Gynecology Department, Sanglah Hospital/ Medical Faculty, Udayana University, Indonesia.

****Corresponding Author***

I. Introduction

It is estimated that 22,440 people in the United States were diagnosed with ovarian cancer in 2017, with 14,080 succumbing to the disease. The 5-year survival rate is low (20-40%) since most women present at later stages (stages III and IV). Subtypes of ovarian cancer include epithelial ovarian cancer (EOC), germ cell tumors, and sex cord stoma tumors [2]. Histological analysis has revealed that about 90% of ovarian tumors are epithelial in origin, and that EOC is the deadliest form of gynecologic malignancy in women. Standard treatment for EOC consists of cytoreduction followed by platinum-based chemotherapy, and although most patients react well to this approach, up to 80% of patients will experience a disease recurrence, and the median progression-free survival is only 12-18 months [3]. Other kinds of EOC include high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), mucinous carcinoma, endometrioid carcinoma, and clear cell carcinoma. Histotypes have different patterns of occurrence, causes, and therapies. The HGSC subtype of EOC is the most common and aggressive form of the disease [4]. Surprisingly, new findings from next-generation sequencing reveal how intricate the carcinogenesis of EOC actually is. Multiple genetic and epigenetic changes have been found to play a pivotal role in carcinogenesis and progression for specific subgroups of individuals with EOC [5]. In order to enhance the clinical prognosis for EOC patients, it is essential to find a novel target screening approach and therapy strategy.

One recent development in ovarian cancer targeted treatment is the discovery of PARP inhibitors [6]. In cells, PARP inhibitors are triggered when DNA repair has been impeded by the homologous recombination (HR) process. HR deficiency in cells with altered breast-associated cancer antigens (BRCA) function is shown in both BRCA-mutated ovarian cancer (also known as "BRCAness" ovarian cancer) and a significant fraction of non-BRCA mutated ovarian cancer [7]. Germline BRCA mutations (gBRCAm) are estimated to account for 10%-15% of cases of EOC, on average [3]. However, the available data shows that this may be grossly understated, particularly for women with high-grade serous ovarian cancer (HGSOC). Recent studies in molecular and genetics have found that anywhere from 15 percent to 25 percent of HGSCs contain a mutation in the breast cancer-predisposing genes BRCA1 and BRCA2. DNA error repair is present in a wide variety of ovarian cancer histologies. Despite the fact that DNA repair defects are present in over 50% of malignancies, HGSC patients have traditionally been the only ones eligible for PARP inhibitor studies [8].

Several PARP inhibitors are now being tested in clinical settings as EOC treatments. A PubMed and Web of Science literature search were carried out for this review. The terms "PARP inhibitors," "ovarian cancer," "BRCA," and "synthetic lethality" were used, together with their proper nouns. The only available language was English. Additionally, we looked for abstracts from the SGO, ESMO, and ASCO conferences. The keyword "PARP inhibitors" was entered into the ClinicalTrials.gov database to find pertinent clinical trials. Two writers independently retrieved data from clinical studies. The authors' discussions helped to resolve all differences. We want to talk about the various PARP

inhibitors, how they were developed, and how this class of drugs might be used in the future.

II. PARP Inhibitors

A type of nuclear enzyme is PARP. The PARP nuclear superfamily comprises 17 members, with PARP-1 and PARP-2 involved in DNA repair [9]. In 1980, it was discovered that DNA damage activated PARP-1, which had since been shown to be essential for DNA repair through the base-excision repair/single-strand break repair (BER/SSBR) pathway [10].

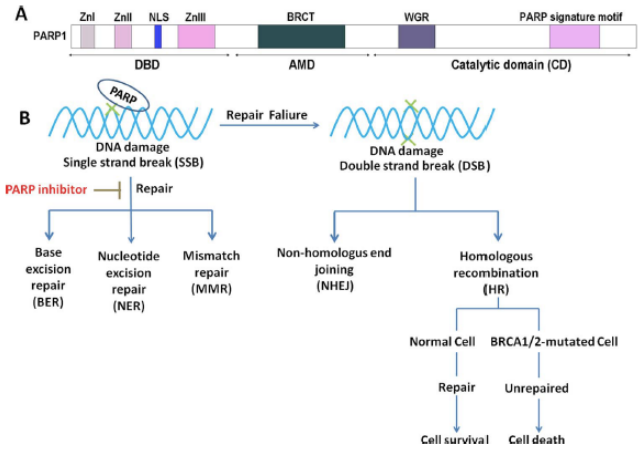

Fig. 1. Summary PARP structure, function, and proposed contribution to synthetic lethality.

Functional domains of PARP-1 include a DNA binding domain (DBD) at the N-terminus, an auto-modification domain in the middle, and a catalytic domain at the C-terminus (CD). The DBD contains three zinc finger motifs. The first two, zincs I and II, facilitate PARP-1's DNA connection by participating in the identification of DSBs and SSBs in DNA (SSB). The DBD's effect on the enzyme's catalytic activity is mediated via the recently found third zinc finger motif (ZnIII), which was previously thought to have no role in DNA binding. In particular, glutamate and lysine residues that function as acceptors for ADP-ribose moieties are found in the BRCT domain of the AMD, which allows it to interact with key DNA damage response proteins. The CD contains the WGR and distinctive melodies, and it acts to stimulate PARP production. The active site, formed by the PARP hallmark motif, binds NAD+ [11]-[13]. (Fig. 1). The fact that nicotinamide and 5-methyl nicotinamide competed with NAD+ as a PARP substrate led to the development of 3-aminobenzamide (3-AB), the first PARP inhibitor, 30 years ago. In the following discussion of PARP inhibitors in cancer therapy [14], we will discuss the creation of selective, efficient, and safe PARP inhibitors, which has recently arisen as a hot subject in the PARP research area.

III. BRCA Mutation and DNA Repair

In order to operate properly, cells must be able to repair DNA damage in a precise and efficient manner while also preventing genomic instability. At least five key DNA damage repair operating systems are present in mammalian cells, including BER, nucleotide excision repair (NER), and mismatch repair (MMR) [15], [16]. Homologous recombination (HR) and nonhomologous end joining (NHEJ) are two mechanisms for repairing DNA double-strand breaks (DSBs) [17]. Some of the most severe forms of DNA damage are single-strand breaks (SSBs) and double-strand breaks (DSBs), both of which can lead to genomic instability, cell death, and cancer if they go unrepaired. Partial-Sequence Bloc (SSB) binding protein 1 (PARP-1) is an enzyme present in nuclei that has been shown to recruit other enzymes involved in DNA repair to SSBs in DNA [18]. DNA replication can be disrupted by DSBs caused by SSBs that aren't repaired. Thus, PARP inhibitors can exacerbate preexisting DNA damage. However, double-strand breaks (DSBs) are common during each cell cycle and can be repaired by HR processes. HR repair (HRR) consists of a number of proteins, including the well-known BRCA1 and BRCA2 [19]. (Fig. 1). BRCA1 contributes to the HRR-dependent signaling and repair of DNA double-strand breaks. BRCA1 is involved in transcription regulation and cell-cycle checkpoint management, whereas BRCA2 has a more direct repair involvement in HRR through its reliance on the regulation of Rad51 (as shown by the formation of a BRCA2-Rad51 complex that binds to the exposed DNA; see [20]). Considering the essential roles played by BRCA1 and BRCA2, it stands to reason that a deficiency in either gene would lead to a defective HRR and that inability to execute DNA DSB repair would eventually lead to cell death [21].

Specific information on the BRCA genes is available, with the BRCA1 gene (representing breast cancer susceptibility) being confirmed in 1990 [22]. Stratton and Wooster, working at the Institute of Cancer Research in London, UK, independently discovered the BRCA2 gene in the same year [23]. The identification of these genes was a major step forward in the management of families affected by breast and ovarian cancer since it allowed for BRCA mutation screening, genetic counselling, risk assessment, and therapy [24]. If a woman inherits a mutation in BRCA1 or BRCA2, she has a 40% probability of developing ovarian cancer and a 20% chance of acquiring breast cancer [25]. Germline (g) BRCA mutations have been estimated to account for 10%-15% of ovarian cancer cases in the past [26]. For HGSOC patients in particular, it is hypothesized that these numbers are drastically low [17]. Furthermore, 17% of women with HGSOC were discovered to have a BRCA mutation, and almost half (44%) of these patients did not have a family history of malignancy [27]. The aforementioned findings advocate for testing for BRCA mutations in all individuals with HGSOC, regardless of family history. BRCA testing needs to move away from the traditional genetic service routes and toward a more streamlined oncology-focused genetic testing service [17], as opposed to the current system in which patients are tested and referred based on family history. In addition, at the start of April 2005, Nature published two publications describing the exceptional in vitro sensitivity of BRCA-mutated cells to treatment with a specific inhibitor of PARP. These publications markedly ushered in a new era in the study of targeted therapy and introduced the therapeutic strategy of EOC into clinical practice [28], [29].

IV. Synthetic Fatality

Using an inhibitor of a DNA-repair enzyme to preferentially kill tumor cells with poor HR is a unique notion in cancer treatment that has emerged in recent years in the absence of an external chemical that breaks DNA. This concept serves as an example of synthetic lethality, which occurs when many factors, including mutation and gene silencing, lead to cell death at the same time [16]. When a gene or protein flaw that is ordinarily safe joins with another gene or protein issue, it might be deadly to some cells, a phenomenon known as synthetic lethality [16]. Cells with defective HR are particularly susceptible to PARP inhibition, as they rely on NHEJ and single-strand DNA repair. Blocking PARP activity causes replication forks to stall, leading to an increase in double-strand breaks (DSBs), which can lead to genetic chaos and cell death (through senescence or apoptosis) [17]. Mutations in BRCA1/2 and other homologous recombination proteins, including as ATM, RAD51D, CHEK1, CHEK2, and CDK12, have been reported to enhance susceptibility to PARP inhibition in both in vitro and in vivo studies [17], [18]. As was mentioned before, a lack of BRCA1 or BRCA2 activity renders cells very vulnerable to PARP inhibition, which in turn triggers apoptosis. Conclusions from clinical studies have provided strong support for the hypothesis that BRCA1/2 mutations in vitro result in synthetic lethality due to PARP inhibitors [17]. Given its increasing therapeutic relevance, studies of this synthetic lethality should be continued, ideally using in vivo or clinical trial methods.

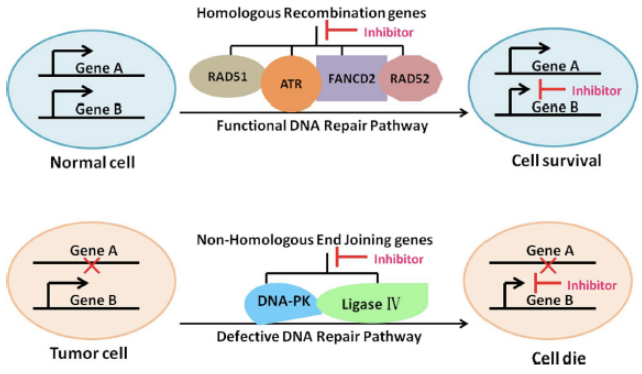

Fig. 2. A synthetic lethal approach to tumor therapy.

Recently, it was discovered that DSBR genes are critical therapeutic targets in cancer treatment, and this was accomplished by applying the synthetic lethality approach. The development of a small number of novel cancer inhibitors may arise from targeting the HR and NHEJ pathways (Fig. 2). There are currently several compounds available that can impede DNA repair processes. The DNA stand exchange activity of RAD-51 is selectively blocked by the small molecule inhibitor B02 [18]. Because of its ATR inhibitory properties, NU6027 has been shown to suppress the expansion of RAD51 foci and to have a synthetic lethal relationship with BER inactivation in an ovarian cancer cell line [19]. HR is assisted in resuming stalled replication forks by a protein known as RAD52 [19]. DNA-dependent protein kinase (DNA-PKcs), which is involved in the NHEJ pathway, is a therapeutic target for cancer [19]. It has been shown that the chemical SCR7 inhibits NHEJ in a Ligase IV-dependent manner in a mouse tumor model [19], [20]. Accordingly, molecular inhibitors linked to synthetic lethality may have considerable therapeutic promise in the creation of novel cancer regimens.

V. The Creation of PARP Inhibitors for Cancer Treatment

The rapid development of PARP inhibitors like Olaparib, Niraparib, Veliparib, Racaparib, and Talazoparib for the treatment of EOC in clinical settings as either a single agent or in combination with other drugs is allowing for earlier and more effective therapy of this cancer.

A. Olaparib

More studies have been conducted on the PARP inhibitor Olaparib. Proof of concept for PARP inhibition was initially reported after a phase 1 study of Olaparib exhibited a response rate of 47 (9/19) in patients with a germ line BRCA1 or BRCA2 mutation who had breast, prostate, or ovarian cancer [20].

Patients with severely pretreated EOC, the vast majority of whom had an inherited BRCA1/2 mutation, were later shown to benefit with olaparib. There was a significant positive correlation between platinum-sensitive disease and Olaparib-sensitive disease, with a clinical benefit rate of 69% in patients with platinum-sensitive disease, 45% in patients with platinum-resistant disease, 23% in patients with platinum-refractory disease, and 23% in patients with platinum-refractory disease. The most pressing question that ensued from these shocking results was whether or if the effects of Olaparib changed according to BRCA-mutation status [21]. A phase 2 study of Olaparib monotherapy in women with or without BRCA mutations and breast or ovarian cancer was done in 2011 [21].

This suggests that PARP inhibitors may also have a significant effect on the non-BRCA or wild-type (wt) BRCA subgroup of ovarian malignancies. 256 patients with platinum-sensitive recurrent illness were included in the significant phase 2 study Study-19 [21], in which they were randomly assigned to receive either Olaparib as a single agent or a placebo following platinum-based treatment. Maintenance doses of 400 mg of olaparib were given twice daily to this group. The median PFS rose from 4.8 to 8.4 months, and the therapy was well tolerated by most patients. Subgroup analysis of PFS showed that patients in the Olaparib group had a lower risk of progression. The majority of participants' BRCA mutation status was initially unknown, and the study did not actively seek out participants with this mutation (64 percent). In addition, a retrospective trial saw 136 individuals administered Olaparib and 129 patients given a placebo. The BRCA status of 131 (96%) of patients in the Olaparib group was known, compared to 123 (95%) of individuals in the placebo group. Compared to the general population, 74 (56%) of these people have a known or likely harmful germline or tumor BRCA mutation, as opposed to just 50% who do. Median progression-free survival (PFS) was considerably longer in the Olaparib group than in the placebo group among patients with a BRCA mutation (11.2 months vs. 4.3 months), and similar results were shown in individuals with wild-type BRCA, while the difference

between groups was less (7.4 months vs 5.5 months). At the second interim analysis [21], there was no statistically significant difference in overall survival based on BRCA status.

Remarkably, in December, the European Medicines Agency (EMA) approved Olaparib for use as a maintenance treatment in patients with platinum-sensitive, replased, BRCA-mutant (germ line or somatic), HGSOC. Also, individuals with recurrent, germ line BRCA-mutated, advanced-stage ovarian cancer who have previously been treated with three or more courses of chemotherapy are now able to take Olaparib. Patients with ovarian cancer are now being selected for biomarker-directed therapy in clinical practice, which is a huge step forward in the treatment of this disease. This is because of the discovery that these mutations in BRCA1 and BRCA2 greatly increase the risk of the cancer returning.

B. Niraparib

Niraparib, a PARP-1/2 inhibitor, inhibits cancer cell proliferation in animal models with BRCA or PTEN functional loss. The initial human study consisted of a dose-escalation cohort of 60 patients with advanced solid tumors who were also carriers of the BRCA1 and BRCA2 hereditary mutations. Throughout the course of the dose-finding process, the MTD was determined to be 300 mg/day. Dose-limiting toxicities (DLT) included grade 4 thrombocytopenia, grade 3 fatigue at 30 mg/day, and a case of grade 3 pneumonitis at 60 mg/day. Phase 1 of the study included 49 participants with ovarian or peritoneal cancer. The response rate for these patients with gBRCA ovarian cancer who received dose-escalation treatment between 80 and 400 mg/day was 40%, and the median time to response was 387 days (range 159-518). This cohort of patients with gBRCA ovarian cancer showed a 50% response rate in the platinum-sensitive scenario, compared to a 33% response rate in the platinum-resistant situation. Furthermore, two patients with platinum-resistant and platinum-refractory ovarian cancer both achieved disease stability for greater than 16 weeks during the course of the study [22].

Moreover, 22 patients in the dosage expansion cohort and 5 patients in the dose-escalation cohort of this phase 1 trial were given Niraparib at the 300 mg/day phase 2 dose recommended for sporadic HGSOC. Sixty-seven percent of patients with platinum-sensitive sporadic HGSOC responded to treatment. There was a 16% response rate in patients with sporadic platinum-resistant HGSOC, and another 3 individuals have experienced disease stability for 16 weeks or more [22].

Because it was the first phase 3 study to investigate PARP inhibitors as a maintenance treatment for patients with ovarian cancer [22], the ENGOT-OV16/NOVA trial was a landmark clinical trial. A recurrence of platinum-sensitive ovarian cancer was present in these patients, as defined by disease progression more than six months after the penultimate platinum-based therapy. Two prior cycles of platinum-based chemotherapy are required. Testing by NOVA Participants were divided into two groups (the gBRCA cohort and the non-gBRCA cohort) depending on whether or not they carried a germline mutation in the BRCA genes (Myriad Genetics). After completing their final dose of platinum-based therapy, patients were randomly assigned to receive either Niraparib (300 mg) or placebo once daily for 28 days (with no treatment interruptions) until disease progression or unacceptable toxicity. The median progression-free survival for patients treated with Niraparib was considerably higher than that of the placebo group. For patients with HRD tumors, survival was 12.9 months in the non-gBRCA cohort compared to 3.8 months in the gBRCA cohort (hazard ratio, 0.38; 95 percent CI, 0.24) and 21.0 months in the gBRCA cohort compared to 5.5 months in the non-gBRCA cohort (hazard ratio, 0.45; 95 percent CI, 0.34-0.61). Patients with platinum-sensitive, recurrent ovarian cancer had a longer median progression-free survival (PFS) when treated with Niraparib, independent of gBRCA mutation status or HRD. Furthermore, the toxicity to bone marrow was manageable and low. Clinical trials using niraparib as a maintenance treatment for patients with advanced ovarian cancer who have previously received and responded to first-line platinum-based chemotherapy are now ongoing (NCT02655016, PRIMA). PRIMA enrolls participants based on the existence of a positive HRD test, as opposed to the gBRCA-focused SOLO1 (NCT01844986). The NOVA study's findings might have an effect on this. Participants in PRIMA must have received at least four cycles of platinum-based chemotherapy. In this third-phase trial, individuals are assigned a 50-50 chance of receiving Niraparib or a placebo. We expect to get the outcomes in March of 2018. Niraparib was tested in persons with ovarian cancer who had already undergone three or four courses of chemotherapy in the QUADRA study, a single-arm phase 2 research. Currently, this trial is being held (NCT02354586).

C. Veliparib

Veliparib is a PARP1/2 inhibitor that is a tiny molecule that may be used orally. There was a lot of good news for this PARP inhibitor from phase 1 trials. Significant myelosuppressions were observed when Veliparib was used with DNA-damaging medications (cyclophosphamide, topotecan, and doxorubicin). Based on the results, the minimum recommended daily dosage of veliparib for combination treatment is 60 mg [23].

A phase 2 study [24] found that veliparib treatment was effective in treating ovarian cancer caused by BRCA mutations. Sixty percent of 50 women with ovarian cancer who had only undergone three or fewer chemotherapy treatments were found to have developed resistance to platinum. For disorders that are resistant to platinum, the response rate was 20%, while it was 35% for those that were susceptible to the metal. Overall, 26% of people participated in the survey. Nausea, vomiting, and anemia were the most reported symptoms of grade 2. Symptoms of neutropenia, exhaustion, and nausea were all considered to be of a grade 3 severity.

D. Racaparib

The Food and Drug Administration has designated rucaparib as a breakthrough medicine for the treatment of women with BRCA-mutated ovarian cancer in the later stages of the disease. It is an orally administered, extremely efficient PARP inhibitor. Early clinical activity was shown in the first phase 1 study at a dose of 600 mg twice daily [24] in patients with platinum-sensitive and platinum-resistant ovarian and

peritoneal cancers.

ARIEL-2 is an open-label phase 2 study of Rucaparib's effectiveness in patients with platinum-sensitive, recurrent HGSOC [25]. This study is the first of its kind to prospectively examine sensitivity to Rucaparib. During ARIEL-2 enrolment, the Foundation Medicine T5 next-generation sequencing assay was used to calculate the percentage of genetic loss of heterozygosity (LOH) in both archived and pretreatment samples (Foundation Medicine, Cambridge, MA, USA). They determined a cutoff of 14 percent or more to define LOH high based on assessments of The Cancer Genome Atlas (TCGA) microarray and survival data for patients with ovarian cancer who had received platinum-based treatment. Tumor analysis was used to classify patients into one of three predetermined HRD subgroups: those with BRCA mutations (germline or somatic deletions; n = 40), those with BRCA wild-type but high levels of copy number loss (n = 82), and those with BRCA wild-type but low levels of copy number loss (n = 70). Twenty-four patients in the BRCA mutant group, fifty-six in the loss of heterozygosity (LOH) high group, and fifty-nine in the LOH low group had illness progression or death. Median progression-free survival (PFS) after Rucaparib therapy was 12.8 months (95 percent CI, 9.0-14.7) in the BRCA mutant sample, 5.7 months (5.3-7.6) in the LOH high subgroup, and 5.2 months (5.2-5.6) in the LOH low cohort (3.6-5.5). PFS was significantly higher in the BRCA mutant and LOH high groups than in the LOH low category [25]. Overall, 82 percent, 43%, and 22 percent of the BRCA1/2-mutant, BRCA-like, and biomarker-negative groups responded to treatment according to RECIST and CA125 response criteria, with a median progression-free survival (PFS) of 286 days, 216 days, and 111 days, respectively. Two other prospective molecular stratification of patients were used in ongoing ovarian cancer trials: ARIEL2, a single-arm study in patients with high-grade ovarian cancer who have received at least three prior chemotherapy regimens, and ARIEL3, a randomized maintenance study of rucaparib vs. placebo in patients with HGSOC who have received at least two lines of platinum regimens.

E. Talazoparib

In preclinical settings, the PARP1/2 inhibitor talazoparib specifically targets tumor cells with the BRCA1/2 mutation. Its potency exceeds that of other PARP-1/2 inhibitors including Olaparib, Rucaparib, and Veliparib by a factor of 20 to 200 [25]. 39 individuals were included in the phase 1 dosage-escalation research, which involved nine cohorts, and were given doses ranging from 25 to 1100 mg daily. As a consequence, the maximum tolerated dose was determined to be 1000 mg daily. 17 patients with high-grade ovarian cancer that was BRCA1/2-mutant were treated with dosages of at least 100 g daily. Fatigue, nausea, anemia, neutropenia, and thrombocytopenia were some of the adverse reactions that could have been connected.

Talazoparib's potential role in patients with BRCA1/2-associated ovarian cancer who have previously received PARP inhibitor therapy is being investigated in a phase 2, single-arm research (NCT02326844). Patients must be eligible if they previously had PARP inhibitor monotherapy and progressed after achieving a response (complete response, partial response, or stable disease for less than four months). This study tackles the crucial question of whether repeating the experiment using a different PARP inhibitor will result in a greater clinical response.

VI. Companions for PARP Inhibitors Diagnostics

Because PARP inhibitors have been rapidly adopted in clinical practice, companion diagnostics (CDx) are crucial for determining which patients may benefit from them. The detection of related gene alterations for PARP inhibitor applications is now supported by three major types of technology [26]. One, BRACAnalysis CDxTM from Myriad is the only FDA-approved test for determining whether a patient is a candidate for treatment with Olaparib or Veliparib. Currently, (2) myChoice HRDTM is being used in combination with the development of niraparib (3) to diagnose patients with EOC. Foundation Medicine employs rucaparib in conjunction with their NGS-based CDx to detect BRCA-like signatures in cancer (FoundationOneTM). Unlike other methods for identifying gBRCA mutations, BRACAnalysis CDxTM does not rely on next-generation sequencing (NGS) to do so. Instead, it employs two in vitro assays, BRACAnalysis CDx Sanger Sequencing for sequence variants and the BRACAnalysis CDx Large Rearrangement Test for large rearrangements [26]. Variants are presently classified as one of five types: harmful, assumed deleterious, variant of uncertain consequence, favor polymorphism, or polymorphism.

MyChoice HRD from Myriad is a next-generation sequencing (NGS)-based diagnostic that detects LOH beyond BRCA and quantifies genomic scarring (HRD Score). Grades for tumors range from 0 (not cancerous) to 100 (very cancerous). High HRD is defined as a score below 42, whereas high HRD is defined as a score over 42 [27]. Massively parallel DNA sequencing is used in foundational medicine to identify therapeutically relevant genomic alterations in cancer genes. In contrast to BRACAnalysis CDx, FoundationOneTM use tumor tissue that has been previously formalin-fixed and paraffin-embedded for archiving purposes. Unlike other methods, FoundationOne can detect significant indel with only a small fraction of tumor tissue and without need a matched normal sample, making it ideal for clinical usage. FoundationOne also offers access to needle and core biopsies. The ARIEL2 study used a BRCA-like signature to identify tumors in patients with EOC by using a modified NGS-based CDx to develop an HRD LOH threshold [27].

VII. The Use of PARP Inhibitors in Clinical Practice

When considering the use of PARP inhibitors in clinical practice, physicians are most concerned with learning how to identify patients who will react to these drugs. Because of the absence of a comprehensive knowledge of how PARP inhibitors function, BRCA1/2 mutation status has been the most studied predictor of medication susceptibility to date. Responses of sporadic high-grade serous ovarian cancer (HGSOC) to PARP inhibitor monotherapy demonstrate that tumor morphologies can yield approximative predictions, but

at lower rates than for BRCA1/2 mutant ovarian cancer. When PARP medications are taken alone in the relapsed setting, the objective response rate for BRCA1/2 mutant ovarian cancer is 30% to 45%. BRCA1/2 mutant HGSOC had a higher response rate compared to platinum-resistant or -refractory groups. Responses in platinum-resistant illness suggest that PARP inhibitors may help certain patients with EOC who have resistant or refractory disease [27], [28].

Different responses to PARP inhibitors were reported in individuals with EOC who carried a detrimental BRCA1/2 mutation. Consequently, somatic mutations in BRCA1/2 mutant cancer cells can re-establish protein expression, re-establish HR, and confer resistance to PARP inhibitors and platinum. In individuals with EOC who had harmful BRCA1/2 mutations, these consequences were seen. Previous studies found that roughly 45% of patients with recurrent platinum-resistant BRCA1/2 mutant ovarian cancer also had secondary somatic mutations [5]. Some mutant BRCA alleles produce proteins with promise but limited stability. Stabilization of these mutant proteins can provide resistance to PARP inhibitors and restore HR even in the absence of a second BRCA mutation. Likewise, BRCA mutant cells with reduced expression of 53BP1 may nevertheless pass on resistance to PARP drugs and reestablish HR [29].

New clues for predicting PARP inhibitor resistance in the treatment of ovarian cancer can be gleaned from the level of understanding of PARP biology and HRD. [29] Despite the promising results to far, we believe there are still numerous unresolved challenges and impediments to the clinical usage of PARP inhibitors. Germline or somatic BRCA1/2 mutations have been the most extensively studied potential response markers to PARP inhibitors. Currently, not all genes affecting DNA repair are known; therefore, a DNA repair capacity test that could be employed in clinics would greatly accelerate the identification of malignancies that are amenable to PARP inhibitor therapy. Preliminary findings from patient-derived xenografts from the ARIEL2 trial suggest that a test employing loss of heterozygosity to assess genomic scarring may be useful for predicting the response to PARP inhibitors in ovarian cancer without BRCA1/2 mutations. Clinical detection of PARP inhibitors now relies on the assay of genomic scarring rather than the previously used static techniques (immunohistochemistry or immunofluorescence) [30].

It is also crucial to consider the increased toxicities of chemotherapy when deciding whether to deliver PARP inhibitors to EOC patients with BRCA1/2 mutations in a clinical context. Platinum-sensitive EOC patients with BRCA1/2 mutations at our institution have olaparib as their first choice for maintenance treatment. Given the established link between BRCA1/2 mutations and sensitivity to PARP inhibitors, we advise that all patients with HGSOC receive BRCA1/2 screening regardless of their family history of hereditary cancers.

VIII. Conclusion

Therapeutically, patients with ovarian cancer caused by BRCA mutations stand to benefit greatly from the progress made in the creation of PARP inhibitors. Patients with ovarian cancer who have the BRCA mutation can now get standard PARP inhibitor treatment. Therefore, doctors treating patients with HGSOC should be aware of the importance of determining whether such patients carry the BRCA1/2 mutation. The degree to which the cancer genome was damaged during testing may also be quantified using loss of heterozygosity (LOH) analysis; more LOH is associated with a more favorable therapeutic response. Due to this unmet need, BRCA1/2 testing and LOH analysis should be a standard part of the inquiry for patients with advanced-stage epithelial ovarian cancer. The results of these tests might have a profound impact on the clinical care of these patients.

Conflict of Interest

Authors declare that they do not have any conflict of interest.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin*. 2017; 67(1): 7-30.
[2] George SH, Garcia R, Slomovitz BM. Ovarian Cancer: The Fallopian Tube as the Site of Origin and Opportunities for Prevention. *Front Oncol*. 2016; 6: 108.
[3] Papa A, Caruso D, Strudel M, Tomao S, Tomao F. Update on Poly-ADP-ribose polymerase inhibition for ovarian cancer treatment. *J Transl Med.* 2016; 14: 267.
[4] Karakasis K, Burnier JV, Bowering V, Oza AM, Lheureux S. Ovarian Cancer and BRCA1/2 Testing: Opportunities to Improve Clinical Care and Disease Prevention. *Front Oncol*. 2016; 6: 119.
[5] Banerjee S, Kaye SB. New strategies in the treatment of ovarian cancer: current clinical perspectives and future potential. *Clin Cancer Res*. 2013; 19(5): 961-8.
[6] Ang YLE, Tan DSP. Development of PARP inhibitors in gynecological malignancies. *Curr Probl Cancer*. 2017; 41(4): 273-286.
[7] Gibson BA, Kraus WL. New insights into the molecular and cellular functions of poly(ADP-ribose) and PARPs. *Nat Rev Mol Cell Biol.* 2012; 13(7): 411-24.
[8] George A, Kaye S, Banerjee S. Delivering widespread BRCA testing and PARP inhibition to patients with ovarian cancer. *Nat Rev Clin Oncol.* 2017; 14(5): 284-296.
[9] Scott CL, Swisher EM, Kaufmann SH. Poly (ADP-ribose) polymerase inhibitors: recent advances and future development, *J. Clin. Oncol*. 2015; 33(12): 1397-1406.
[10] Langelier MF, Servent KM, Rogers EE, Pascal JM. A third zinc-binding domain of human poly(ADP-ribose) polymerase-1 coordinates DNA-dependent enzyme activation. *J Biol Chem*. 2008; 283(7): 4105-14.
[11] Tao Z, Gao P, Hoffman DW, Liu HW. Domain C of human poly(ADP-ribose) polymerase-1 is important for enzyme activity and contains a novel zinc-ribbon motif. *Biochemistry*. 2008; 47(21): 5804-13.
[12] Plummer R. Perspective on the pipeline of drugs being developed with modulation of DNA damage as a target. *Clin Cancer Res.* 2010; 16(18): 4527-31.
[13] Chen Y, Zhang L, Hao Q. Olaparib: a promising PARP inhibitor in ovarian cancer therapy. *Arch Gynecol Obstet*. 2013; 288(2): 367-74.
[14] Davar D, Beumer JH, Hamieh L, Tawbi H. Role of PARP inhibitors in cancer biology and therapy. *Curr Med Chem*. 2012; 19(23): 3907-21.
[15] Sonnenblick A, de Azambuja E, Azim HA Jr, Piccart M. An update on PARP inhibitors--moving to the adjuvant setting. *Nat Rev Clin Oncol*. 2015; 12(1): 27-41.
[16] Gudmundsdottir K, Ashworth A. The roles of BRCA1 and BRCA2 and associated proteins in the maintenance of genomic stability. *Oncogene.* 2006; 25(43): 5864-74.
[17] Jones P, Wilcoxen K, Rowley M, Toniatti C. Niraparib: A Poly(ADP-ribose) Polymerase (PARP) Inhibitor for the Treatment of Tumors with Defective Homologous Recombination. *J Med Chem*. 2015; 58(8): 3302-14.
[18] Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, et al. Linkage of early-onset familial breast cancer to chromosome 17q21. *Science.* 1990; 250(4988): 1684-9.

[19] Wooster R, Neuhausen SL, Mangion J, Quirk Y, Ford D, Collins N, et al. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science.* 1994; 265(5181): 2088-90.
[20] Audeh MW. Novel treatment strategies in triple-negative breast cancer: specific role of poly(adenosine diphosphate-ribose) polymerase inhibition. *Pharmgenomics Pers Med.* 2014; 7: 307-16.
[21] Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol*. 2007; 25(11): 1329-33.
[22] Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Kwan E, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. *Am J Hum Genet*. 2001; 68(3): 700-10.
[23] Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J Clin Oncol.* 2012; 30(21): 2654-63
[24] Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature.* 2005; 434(7035): 917-21.
[25] Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumors with inhibitors of poly(ADP-ribose) polymerase. *Nature.* 2005; 434(7035): 913-7.
[26] Evans U. Matulonis, PARP inhibitors in ovarian cancer: evidence, experience and clinical potential, *Ther. Adv. Med. Oncol.* 2017; 9(4): 253-267.
[27] Kaelin WJ. The concept of synthetic lethality in the context of anticancer therapy, *Nat. Rev. Cancer.* 2005; 5(9): 689-698.
[28] Hoeijmakers J. Genome maintenance mechanisms for preventing cancer. *Nature.* 2001; 411(6835): 366-374.
[29] Loveday C, Turnbull C, Ramsay E, Hughes D, Ruark E, Frankum JR, et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. *Nat Genet*. 2011; 43(9): 879-882.
[30] Bajrami I, Frankum JR, Konde A, Miller RE, Rehman FL, Brough R, et al. Genome-wide profiling of genetic synthetic lethality identifies CDK12 as a novel determinant of PARP1/2 inhibitor sensitivity. *Cancer Res.* 2014; 74(1): 287-297.
[31] Ke Y, Zhang J, Lv X, Zeng X, Ba X. Novel insights into PARPs in gene expression: regulation of RNA metabolism. *Cell Mol Life Sci*. 2019; 76(17): 3283-3299.