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PARP Inhibitors: On the Horizon of Tailored and Personalized Therapies for Epithelial Ovarian Cancer

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Abstract

Purpose of review—Management of the epithelial ovarian cancer (EOC) remains a therapeutic challenge, with continued poor overall survival. Given low chemotherapy response rates for recurrent disease and short survival times, new treatment options with improved therapeutic indices for targeting cancer's vulnerability are urgently needed in this patient population.

Recent findings—In this review, we summarize the recent development and clinical evaluations of inhibitors of poly (ADP-ribose) polymerase (PARP) as novel targeting agents for EOC. PARP inhibitors exploit synthetic lethality to target DNA repair defects in hereditary breast and ovarian cancer.

In recent clinical trials, EOC patients with BRCA mutations exhibited favorable responses to the PARP inhibitor olaparib compared with patients without BRCA mutations. Additionally, olaparib has been reported to augment the effects of cisplatin and carboplatin on recurrence-free survival and overall survival in mice bearing BRCA1/2-deficient tumors.

Given that hereditary EOC with deleterious BRCA1/2 mutations and BRCAness sporadic EOC are profoundly susceptible to synthetic lethality with PARP inhibition, it is imperative to identify a population of EOC patients that are likely to respond to PARP inhibitors. Recent studies have identified the gene expression profiles of DNA repair defects and BRCAness which predict clinical outcomes and response to platinum-based chemotherapy in EOC patients.

Summary—Ovarian cancer continues to carry the highest mortality among gynecologic cancers in the Western world. Clinical development of PARP inhibitors that target DNA repair defects in cancer is a novel and imperative stride in individualized identification of molecular characteristics in management of ovarian cancer.

Keywords

ovarian cancer; PARP inhibitors; BRCA; overall survival; synthetic lethality

Introduction

Ovarian cancer (EOC) is the second most common gynecologic cancer in the United States, and carries the highest mortality in this category in the Western world, with 13,850 women dying from this disease yearly (1). Despite multiple new approaches to treatment, the high mortality rates from EOC have remained largely unchanged for many years, with a 5-year

overall survival of only 30% to 39% (2). Based on multiple studies, the standard of care for patients with advanced ovarian cancer is maximal surgical cytoreduction, followed by platinum-containing chemotherapy, usually comprised of carboplatin and paclitaxel (3–5). However, despite high overall response rates being 60–75% with initial therapy, the majority of women with EOC will relapse and require retreatment with platinum-based chemotherapy regimen (6). The progression free survival and overall survival depend greatly on the tumor sensitivity to a platinum chemotherapy. For patients who become resistant to a platinum-based chemotherapy (defined as persistent or progressive disease during, or recurrence within 6 months after completing a platinum-based regimen), response to other cytotoxic chemotherapeutic regimens is low, with response rates of only 6–30% (7). Topotecan and liposomal doxorubicin are currently among second line therapy choices for platinum resistant ovarian cancer with objective response rates (RRs) of approximately 10% to 15% in platinum-resistant patients with the median progression-free survival of 9.1–13.6 weeks and overall survival of 35.6–41.3 weeks (8). Given these low response rates and short survival times with current standard EOC regimens, development of tailored therapies on the basis of biomarker screening for predictive therapeutic outcomes is urgently needed for the future EOC treatment. In this review, we summarize the recent development and clinical evaluations of inhibitors of poly (ADP-ribose) polymerase (PARP) as novel targeting agents for EOC. To achieve the full potential of these new agents and to prevent emergence of drug resistance, appropriate selection of the patient population is imperative. Ongoing and future potential approaches for implementing such tailored therapeutic regimens based on genetic or biomarker screening will also be discussed in this review.

PARP Inhibitors and Synthetic Lethality

PARP inhibitors belong to a new class of agents that exploit synthetic lethality to target DNA repair defects in hereditary breast and ovarian cancer. Synthetic lethality is based on the concept that loss of function in both genes leads to cell death whereas loss of function in either of these genes alone permits survival (9). Targeted inhibition of a gene that functionally compensates for the defective gene in a synthetic lethal pair is postulated to selectively kill cancer cells while sparing normal tissue. This strategy potentially provides the leverage of a wider therapeutic window than conventional chemotherapeutic approaches.

The best example of the synthetic lethality is the interactions between PARP inhibition and BRCA mutations. PARP1 is an important component of base excision repair (BER) involved in the repair of DNA single strand breaks (SSBs) as a result of endogenous base damage. Inhibition of PARP-1 activity leads to persistent DNA single strand breaks (SSBs). When encountered by the replication forks, the SSBs are converted into DNA double strand breaks (DSBs) (10). Normal cells, proficient in homologous recombination repair (HRR), are able to repair DSBs and survive under the condition of PARP inhibition. However, cancer cells harboring BRCA1 or BRCA2 mutations are defective in HRR and, consequently, susceptible to the synthetic lethality of PARP inhibitors (11, 12).

Hereditary and Sporadic Ovarian Cancers

Hereditary EOC, which accounts for 10–15% of all EOC, predominately affects women with heterozygous germline mutations in BRCA1 or BRCA2 genes. The majority of EOC cases, however, are considered to be non-hereditary and sporadic. BRCA1 and BRCA2 tumor suppressor genes serve as critical components of HRR for the repair of DSBs. Thus, cancer cells deficient in BRCA1 or BRCA2 function are hypersensitive to DNA damaging agents that cause DSBs, such as PARP inhibitors and platinum drugs. BRCA1 plays a multifaceted role in the regulation of DNA repair, cell cycle checkpoints, transcription, chromatin remodeling, and ubiquitination (13). Despite its broad roles in DNA damage

response, BRCA1 is necessary for HRR by participation in initial DSB processing. HRR is instigated by the binding of Mre11, Rad50, and Nbs1 (MRN) complex to the ends of DSBs. CDK-mediated phosphorylation of CtIP is required for the formation of MRN-BRCA1-CtIP complex, which promotes end resection of DSBs to generate 3'-single strand overhangs for following HRR process (14, 15). BRCA2 plays a more specific role in the regulation of Rad51 recombinase, a central mediator of HRR. BRCA1 recruits and interacts with BRCA2 through PALB2 (16, 17). Subsequently, BRCA2 loads Rad51 onto 3'-single strand overhangs, which undergo invasion and copying of homologous sequences in the intact sister chromatid during S and G2 phases of the cell cycle (18). Given that, HRR carries out error-free repair of DSBs. Deficiency in either BRCA1 or BRCA2 function leads to an increased use of error-prone and mutagenic non-homologous end-joining (NHEJ) repair (19). Therefore, loss-of-function mutations in BRCA1 or BRCA2 gene contribute to genome instability which underlies hereditary ovarian carcinogenesis. More recently, mutations in other genes involved in HRR have been identified to contribute to hereditary EOC in the absence of BRCA1/2 mutations. These genes include PALB2, Rad51C, Rad51D, BRIP1, BARD1, Chk2, Mre11A, MSH6, NBN, Rad50, p53 and kras (20–22).

Emerging evidence has led to the notion of the prevalence of defective HRR in a substantial subset of sporadic breast and ovarian cancers. The concept of BRCAness (or BRCAless) is coined to describe the phenotypes of HRR deficiencies in sporadic cancers that share with BRCA1/2-associated hereditary cancers (23). BRCAness phenotypes of sporadic cancers are partly attributable to hypermethylation of BRCA1 promoter (24–26) and somatic mutations of BRCA1/2 (27–29).

Aberrant or impaired regulation of other proteins associated with the HRR pathway is also reported to contribute to a BRCAness phenotype. Down-regulation of one of the Fanconi anemia (FA) proteins, FANCF, by promoter methylation has been identified in sporadic EOC (30, 31). FA proteins functionally converge with the BRCA proteins to regulate HRR-dependent repair of DSBs. Additionally, EMSY gene, which binds to and inactivates BRCA2, is reported to be amplified in 17% of sporadic high-grade EOC (32). Therefore, it is estimated that up to 50% of high-grade sporadic EOC possess the characteristics of BRCAness and can potentially be targeted by PARP inhibitors (33).

PARP Inhibitors versus Platinum-based Chemotherapy

The mechanism of action of platinum drugs such as cisplatin and carboplatin includes formation of adducts with guanine bases of DNA to produce major intrastrand and minor interstrand DNA crosslinks. Nucleotide excision repair (NER) has been considered to play a major role in the repair of platinum-induced crosslinking lesions (34). NER involves the excision of platinum-intrastrand crosslinks followed by the gap-filling of SSBs. However, cumulative evidence indicates that HRR is also required for the repair of platinum-induced DNA damage (35, 36). These observations support that both NER and HRR are involved in the resolution of primary SSB and secondary DSB lesions caused by platinum-DNA crosslinks. Preclinical studies demonstrate that cancer cells with deficiency in BRCA1 or BRCA2 have enhanced sensitivity to platinum drugs (37, 38). This is consistent with clinical findings that women with BRCA1/2-associated EOC have improved overall survival due to a more favorable response to the platinum-based chemotherapy (39–41).

PARP inhibitors cause DNA lesions of replication-associated DSBs as a result of persistent SSBs in proliferating cells. Thus, HRR appears to be the sole mechanism that suffices for the repair of this type of DNA lesion. In a manner similar to that of the platinum sensitivity, BRCA1/2-mutant cancer cells are markedly sensitive to PARP inhibitors, demonstrated by in vitro and in vivo models (42, 43). In phase I and II clinical trials, EOC patients with

BRCA mutations exhibited favorable responses to the PARP inhibitor olaparib (44–46) compared with patients without BRCA mutations (47). This drug was well tolerated in both patient populations (45, 46). Interestingly, post-hoc analyses indicated that clinical response to olaparib correlated with the longest progression-free survival. Thus, olaparib exhibited high level of response in patients with platinum-sensitive EOC (44, 47). It appears that PARP inhibitors and platinum drugs share a spectrum of enhanced therapeutic efficacy against BRCA1/2-associated EOC largely due to the inherent deficiencies in HRR for the repair of DSBs. In contrast to the platinum drugs, PARP inhibitors target the genetic defects in the HRR pathway in hereditary and some sporadic EOC, thereby exhibiting greater tumor specificity and minimal toxicity to normal tissues. Furthermore, DNA-crosslinking lesions caused by platinum drugs are potentially mutagenic and therefore promote the phenotypes of platinum/drug resistance after each re-treatment. Therefore, PARP inhibitors should be considered as part of the first line therapy for hereditary and BRCA-associated sporadic EOC in the future. On the other hand, a recent phase II clinical trial has demonstrated that olaparib treatment results in improved progression-free survival in platinum-sensitive, relapsed, high-grade serous EOC, implicating a potential use of this agent as maintenance therapy (48). This finding raises the possibility of sequential use of PARP inhibitors and platinum-based chemotherapy for EOC treatment.

Clinical Development of PARP Inhibitors

The therapeutic potential of the PARP inhibitors has elicited considerable interest in the clinical development of this class of agents. A list of current clinical trials of the PARP inhibitors is compiled in Table 1. To achieve the maximal efficacy of the PARP inhibitors, clinical trials patient groups were mostly enriched for populations of hereditary BRCA1/2-associated tumors. Olaparib (AZD2281; AstraZeneca) appears to lead among the clinical development of PARP inhibitors in EOC. Earlier phase I and II clinical trials substantiate the activity of olaparib as a single agent in BRCA1/2-mutated and platinum-sensitive recurrent EOC (44–47). Main efficacy results of reported clinical trials of olaparib are presented in Table 2. Unfortunately, olaparib will not progress into Phase III trials as the maintenance therapy for serous EOC despite significantly improved progression-free survival. Currently, increasing numbers of clinical trials of olaparib have been conducted in combinations with carboplatin, carboplatin/paclitaxel, or pegylated liposomal doxorubicin (Doxil) in EOC. Veliparib (ABT-888; Abbott) also emerges as a frontrunner of PARP inhibitors. It is under investigation mostly in combinations with various DNA damaging agents such as temozolomide, topotecan, and cyclophosphamide. Combinations of PARP inhibitors and other cytotoxic chemotherapy agents are conceivably based on preclinical findings. Olaparib has been reported to augment the effects of cisplatin and carboplatin as demonstrated by increased recurrence-free survival and overall survival in mice bearing BRCA1/2-deficient tumors (49–51). In addition, veliparib has been shown to potentiate the effects of temozolomide, carboplatin, and cyclophosphamide by delaying the growth of xenograft tumor with BRCA1/2 deficiency (52, 53). The rationale for the use of these chemotherapy drugs in combination with PARP inhibitors is to impose additional DNA damage through different mechanisms in hope of eliminating cancer sub-populations that are resistant to PARP inhibitors.

Challenges for PARP Inhibitors

To date, targeting therapy with PARP inhibitors seems to suffer some setbacks by a lack of highly anticipated activity as single agents, and consequently requires combinations with other conventional chemotherapeutic or novel targeting agents (Table 1). The initial success of PARP inhibitors in preclinical and clinical development is perhaps a best example of the “proof-of-concept” approach to target cancers with inherent or acquired defects in DNA

repair. However, the complexity of tumor heterogeneity has to be factored in to address the problems of sub-optimal responses and emergency of inherent or acquired therapeutic resistance. As mentioned above, deficiencies in BRCA function and the HRR pathway confer profound genome instability in cancers. Therefore, as the disease progresses, these cancer cells tend to evolve into sub-populations, each of which may possess distinct phenotypes with various degrees of response to PARP inhibitors. Mounting evidence has demonstrated that secondary somatic mutations of mutated BRCA1 or BRCA2 gene restore proficiency in HRR and confer resistance to platinum chemotherapy and PARP inhibitors (54–57). These findings provide the underlying mechanism of acquired resistance in platinum-sensitive hereditary BRCA-associated cancers. On the other hand, it is estimated that up to 50% of high-grade serous sporadic EOC harbor the phenotypes of BRCAness which renders enhanced sensitivity to PARP inhibitors. However, whether cancer cells exhibit the BRCAness phenotype throughout the same tumor remains questionable. Therefore, the problems associated with tumor heterogeneity and the prevalence of BRCAness-cancer cells populations collectively pose major challenges for successful clinical development of PARP inhibitors.

Gene Expression Profiling and Biomarker Assays for HRR Deficiencies

Given that hereditary EOC with deleterious BRCA1/2 mutations and BRCAness sporadic EOC are profoundly susceptible to synthetic lethality with PARP inhibition, it is imperative to identify a population of EOC patients that are likely to respond to PARP inhibitors and thus benefit from the therapy. Traditional chemotherapy for EOC treatment uses the “one size fits all” approach using platinum-based regimens as initial therapy without the knowledge of their innate drug sensitivity. This approach will potentially miss the window of opportunity to target PARP inhibitor-sensitive EOC and thus allow development of drug resistant cancer populations. Platinum sensitivity of EOC, as defined largely by the period of progression-free survival, correlates with the responsiveness to PARP inhibitors (44, 47). However, it does not predict the status of HRR.

Gene expression analyses and biomarker functional assays as predictive and prognostic measures for chemosensitivity of EOC have emerged. Using publicly available microarray data, a study on gene expression profiling has been reported to identify the signature of BRCAness that correlates with clinical responses to the platinum drugs in patients with sporadic EOC (58). The BRCAness profile also correlates with deficiencies in HRR and with responsiveness to PARP inhibitors in cell line models. Another study using the same microarray data identifies the expression profile of specific genes involved in DNA repair which predicts clinical outcomes and response to platinum-based chemotherapy in EOC patients (59). These two studies lay the groundwork for establishment of the correlation between genomic/phenotypic landscapes of EOC and clinical outcomes in patients.

Identification of molecular characteristics of BRCA mutations or BRCAness may be technically challenging and often uninformative due to inconsistency from different analytical approaches and heterogeneous tumor/patient populations. Functional biomarker assays for HRR proficiency, the ultimate phenotype of BRCA mutations and BRCAness, are more accurate to predict chemosensitivity of EOC and clinical outcomes. Impairment of DNA damage-induced Rad51 foci formation is indicative of defects in HRR and can be detected using ex vivo assays. A report has demonstrated a strong correlation between decreased Rad51 foci formation and enhanced sensitivity to the PARP inhibitor rucaparib in primary cultures derived from ascetic fluid from EOC patients (60). BRCA1, FANCD2, and Rad51 have also been reportedly used as biomarkers to detect HRR pathway deficiencies in breast tumor biopsies (61). Thus, functional assays of HRR status to predict PARP inhibitor sensitivity in EOC may be feasible as routine clinical/laboratory tests with better accuracy.

Conclusions

Epithelial ovarian cancer continues to carry high mortality rates due to the high incidence of the disease recurrence and subsequent chemoresistance. A novel patient individualized chemotherapeutic approach based on the cancer's genomic characteristics is urgently needed. Synthetic lethality, accounting for loss of function in both genes leading to cell death whereas loss of function in either of these genes alone permits continued survival, is described as a promising concept in ovarian cancer targeting. The best example of the synthetic lethality is the interactions between PARP inhibition and BRCA deleterious mutations or BRCAness phenotype of sporadic ovarian cancer. Appropriate identification of susceptible patient gene characteristics as a predictive and prognostic measure of the efficacy of the PARP inhibitor targeting is paramount.

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Key points

We summarize the recent development and clinical evaluations of inhibitors of poly (ADP-ribose) polymerase (PARP) as novel targeting agents for epithelial ovarian cancer (EOC).

PARP inhibitors belong to a new class of agents that exploit synthetic lethality to target DNA repair defects in hereditary breast and ovarian cancer as well as tumors with BRCAness phenotype.

In phase I and II clinical trials, EOC patients with BRCA mutations exhibited favorable responses to the PARP inhibitor olaparib compared with patients without BRCA mutations.

Olaparib has been reported to augment the effects of cisplatin and carboplatin as demonstrated by increased recurrence-free survival and overall survival in mice bearing BRCA1/2-deficient tumors. In addition, veliparib has been shown to potentiate the effects of temozolomide, carboplatin, and cyclophosphamide by delaying the growth of xenograft tumor with BRCA1/2 deficiency.

Recent studies have identified the gene expression profiles of DNA repair defects and BRCAness which predict clinical outcomes and response to platinum-based chemotherapy in EOC patients.

Given that hereditary EOC with deleterious BRCA1/2 mutations and BRCAness sporadic EOC are profoundly susceptible to synthetic lethality with PARP inhibition, it is imperative to identify a population of EOC patients that are likely to respond to PARP inhibitors and thus benefit from the therapy.

Ongoing and recently completed clinical trials of PARP inhibitors as single agents or in combination with other agents (partial list).

Table 1

PARP inhibitor	Combination	Phase of development	Patient population
Olaparib (AZD2281)	-	II	Known BRCA mutation or recurrent high grade serous ovarian cancer
	-	II	BRCA1 positive advanced ovarian cancer
	-	II	Advanced ovarian cancer with confirmed BRCA1/2 mutation
	-	II	Platinum sensitive relapsed serous ovarian cancer
	Carboplatin	I	Refractory or recurrent ovarian cancer
Veliparib (ABT-888)	Carboplatin	I	BRCA1/2-associated hereditary epithelial ovarian cancer
	Carboplatin	I	BRCA1/2-associated familial ovarian cancer and sporadic ovarian cancer
	Carboplatin/Paclitaxel	II	Platinum-sensitive advanced serous ovarian cancer
	Doxil	II	Advanced BRCA1/2-associated ovarian cancer and failed previous platinum-based chemotherapy
	Cediramib	I/II	Recurrent ovarian cancer
Iniparib (BSI-201)	-	I/II	BRCA-germline mutation and platinum-resistant or partially platinum-sensitive relapsed epithelial ovarian cancer
	Temozolomide	II	Recurrent high grade serous ovarian cancer
	Temozolomide	I	Ovarian cancer with BRCA mutation
	Cyclophosphamide	II	Refractory BRCA-positive ovarian, primary peritoneal or ovarian high-grade serous, fallopian tube cancer
	Carboplatin/Doxil	I	Recurrent ovarian cancer, primary peritoneal or fallopian tube cancer
Rucaparib (PF0136738)	Carboplatin/Paclitaxel/Bevacizumab	I	Newly diagnosed previously untreated epithelial ovarian, fallopian tube or primary peritoneal cancer
	Topotecan	II	Relapsed or refractory ovarian epithelial cancer or primary peritoneal cancer
	-	II	BRCA1/2-associated epithelial, fallopian tube, or primary peritoneal cancer
	Gemcitabine/Carboplatin	I	Platinum-sensitive recurrent ovarian cancer
	Gemcitabine/Carboplatin	II	Platinum-resistant recurrent ovarian cancer
Rucaparib (PF0136738)	-	II	BRCA1/2 mutation carriers with advanced ovarian cancer

Source: www.clinicaltrials.gov

Doxil, pegylated liposomal doxorubicin.

Table 2

Main efficacy results of reported clinical trials of the PARP inhibitor olaparib.

Trials	Patient Populations	No. of Patients	Treatment Arms	Clinical Responses	References
Phase I (Fong et al., 2010)	Germline BRCA1/2 mutations	50	Olaparib: 40–600 mg twice daily (Dose-escalation) Olaparib: 200 mg twice daily (Dose-expansion)	CBR:46%; RD: 28 weeks	44
Phase II (Audeh et al., 2010)	Germline BRCA1/2 mutations	57	Olaparib: 400 mg twice daily Olaparib: 100 mg twice daily	ORR:33%; RD:41 weeks ORR:13%; RD: 38 weeks	45
Phase II (Gelmon et al., 2011)	Known BRCA1/2 status	64	Olaparib: 400 mg twice daily	ORR:41% (BRCA mutations) ORR:24% (w/o BRCA mutations)	47
Phase II (Ledermann et al., 2012)	Platinum-sensitive recurrent or high-grade serous features	265	Olaparib: 400 mg twice daily Placebo	PFS:8.4 months PFS:4.8 months	48
Phase II (Kaye et al., 2012)	Germline BRCA1/2 mutations	97	Olaparib: 200 mg twice daily Olaparib: 400 mg twice daily Doxil: 50 mg/m ² IV	PFS:6.5 months; ORR:25% PFS:8.8 months; ORR:31% PFS:7.1 months; ORR:18%	62

CBR, clinical benefit rate; RD, response duration; ORR, objective response rate; PFS, progression-free survival.