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Review Article

PARP inhibitors for *BRCA* wild type ovarian cancer; gene alterations, homologous recombination deficiency and combination therapy

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Abstract

After a brief summary of the current status of poly-ADP ribose polymerase (PARP) inhibitors for ovarian cancer, we summarize the current status of PARP inhibitors for *BRCA* wild type ovarian cancer, especially regarding gene alterations other than *BRCA*, homologous recombination deficiency (HRD), and combinations. Discussion of gene alterations other than *BRCA* include the results of multiple gene panels studying homologous recombination repair deficiency genes and cancer susceptibility genes, and influences of these alterations on efficacy of PARP inhibitors and cancer susceptibility. Discussions of HRD include the results of phase three trials using HRD assay, the definition of HRD assays, and the latest assays. Discussions of combinations include early phase trial results and ongoing trials combining PARP inhibitors with immune checkpoint inhibitors, anti-angiogenic agents, and triplets.

Key words: PARP inhibitors, *BRCA* wild type, HRD, LOH, genetic counseling

Introduction

Ovarian cancer is the most lethal gynecologic malignancy worldwide. Poly-ADP ribose polymerase (PARP) is a family of proteins involved in several processes, such as DNA repair, genomic stability, and programmed cell death (1). PARP has an important role in the repair of single-strand DNA breaks. PARP inhibitors induce the accumulation of single-strand DNA damage and can result in double-strand breaks. Double-strand DNA breaks normally would be repaired via homologous recombination repair (HRR), which is a complex process involving many proteins, notably BRCA1 and BRCA2. In HRR-deficient tumors, alternative DNA repair by non-homologous end joining, which is a low fidelity repair mechanism, results in cell death. The concept is referred to as synthetic lethality.

Olaparib is the first drug approved as a PARP inhibitor. The first indication was 'third line or later therapy with germline *BRCA* mutation (gBRCAmt) ovarian cancer confirmed by United States Food and Drug Administration (FDA) approved companion diagnostics.' That accelerated approval was based on the results of phase two studies (Study 19 and Study 58). Study19 compared olaparib with placebo as a maintenance therapy for patients with platinum-sensitive recurrent serous ovarian cancer that responded to platinum doublets. Olaparib prolonged median progression-free survival (PFS; 8.4 vs. 4.8 months; hazard ratio [HR] = 0.35; $P < 0.001$) (2). Subgroup analysis revealed that patients harboring gBRCAmt or somatic BRCA1/2 mutations (sBRCAmt) further merited from olaparib (median PFS 11.2 vs. 4.3 months; HR = 0.18; $P < 0.0001$) (3). Study 58 is an open label phase two study for patients with relapsed solid tumor harboring gBRCA1/

2 mt. Among 193 patients in the ovarian cancer cohort, the response rate was 31.1% (4). In both studies, *BRCA* status was a predictive biomarker of olaparib efficacy. Then, in the confirmatory phase three study (SOLO2 study), g/sBRCAmt was one inclusion criterion, and olaparib again improved median PFS (19.1 vs. 5.5 months; HR = 0.30; $P < 0.0001$) (5). This result led to full FDA approval of olaparib in 2017. Olaparib also improved PFS as maintenance therapy for patients with ovarian cancer harboring the gBRCAmt following response to the first-line platinum-based chemotherapy in the SOLO1 study (3-year PFS rate 60% vs 27%; HR = 0.30; $P < 0.0001$) (6). Other PARP inhibitors, such as niraparib and rucaparib, also are approved in the United States and Europe based on pivotal trials, such as NOVA (median PFS, 21.0 vs. 5.5 months; HR = 0.27) (7) or ARIEL3 (median PFS, 16.6 vs. 5.4 months; HR = 0.23; $P < 0.0001$) (8) (Table 1). In both trials, patients without g/sBRCAmt were eligible, and patients with g/sBRCAmt achieved longer PFS than those without it, although results among patients without g/sBRCAmt treated by PARP inhibitors were better than those with placebo. As a result, niraparib and rucaparib are approved by the FDA as 'maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer' regardless of *BRCA* status. Many hypothesis exist to explain the efficacy of PARP inhibitors not harboring the g/sBRCAmt. One possible explanation is a 'chemo-selection.' All of these pivotal trials randomized patients who responded to platinum doublets, because earlier studies of olaparib suggested that platinum-free interval predicts response of olaparib, regardless of *BRCA* mutation status (9). Other possible explanations include gene alterations other than *BRCA*, regarding gene alterations, HRR deficiency (HRD), and combinations with other targeting agents. We herein review and clarify the current status of PARP inhibitors for patients with ovarian cancer having wild type *BRCA* (BRCAwt), regarding gene alterations, HRD, and combination therapy.

Gene alterations other than *BRCA*

As stated above, PARP has an important role in the repair of single-strand DNA breaks and use of PARP inhibitors can result in double-strand breaks, which normally would be repaired via HRR. In HRR-deficient tumors, alternative DNA repair by nonhomologous end joining results in cell death (synthetic lethality).

Some studies identified other related defects beyond *BRCA1/2* alterations, such as mutations of *ATM, BARD1, BRIP1, CHEK2, PALB2, RAD51C, RAD51D*, and so forth. *BRCA1/2* defects are present only in a small portion of patients with high-grade serous ovarian cancer. Whether other HRR-related gene alterations related to response to PARP inhibitors is partly unknown.

Germline and somatic mutations in HRR genes are present in approximately one-third of ovarian cancers and predict a better response to primary platinum chemotherapy and improves overall survival (OS) (10). Platinum sensitivity was demonstrated in 71 of 85 (84%) primary carcinomas with and 95 of 158 (60%) without an identified HRR mutation (germline or somatic). The remainder were platinum-resistant or refractory ($P = 0.0002$). The presence of a germline or somatic HRR gene mutation was associated with significantly better OS for women with stage II–IV carcinomas compared to patients without HRR mutations ($P = 0.0006$, HR = 0.6, 95% confidence interval [CI] 0.4–0.8).

Hodgson DR et al. (3) reported a Study19 sub-analysis showing that ovarian cancer patients with tumors harboring loss-of-function mutations in HRR genes other than *BRCA1/2* may constitute a small, molecularly identifiable, and clinically relevant population who derive treatment benefit from olaparib similar to patients with gBRCAmt. The data suggest that olaparib is associated with a greater PFS benefit in HRR-mutated patients without the gBRCAmt (HR = 0.21; 95% CI, 0.04–0.86) than in patients with no detectable gBRCAmt or HRR mutation (HR = 0.71; 95% CI, 0.37–1.35) who received olaparib.

Germline mutations of HRR genes also have been implicated in genetic susceptibility to solid tumors. Patients or siblings are recommended specific surveillance and/or risk-reducing surgery if pathogenic/likely pathogenic variants are found in these genes. However, some genes are known to show intermediate penetrance. As summarized in Table 2, *BRIP1* (11), *RAD51C* (12), and *RAD51D* are known for increased lifetime risk of ovarian cancer. *ATM* (13), *BARD1*, *CHEK2* (14,15), and *PALB2* (16) are known for increased risk of breast cancer. For many of these genes, there are limited data on the degree of cancer risk and no clear guidelines on management for carriers of pathogenic/likely pathogenic variants.

Recently, the gene mutations may be tested for concurrently via multigene panel testing (Table 3, Supple Table). However, there is increased likelihood of finding variants of unknown significance in multigene panel testing. In addition, risk management recommendations for these genes should consider clinical factors and family history. This is why multigene testing should be offered in the context of professional genetic expertise for genetic counseling.

HRD assay

The HRD assay is another promising biomarker to predict the efficacy of PARP inhibitors. Two different types of HRD assays, Myriad HRD assays and Foundation Focus, were used for the NOVA and ARIEL3 trials. Myriad HRD assays consist of three different aspects of genomic instability: number of telomeric allelic imbalances (TAI), loss of heterozygosity (LOH) (17), and large-scale state transitions (LSTs). HRD status was defined as HRD-positive for tumors with HRD scores ≥ 42 or a BRCA1/2 mutation. HRD-negative was defined as tumors with HRD scores < 42 and wild type *BRCA1/2*. Foundation Focus detects the presence of sBRCAmt. The laboratory test also can be used to detect the percentage of LOH in tumor tissue samples. Both assays also are predictive for

Table 1. Pivotal randomized trials of PARP inhibitors for platinum-sensitive recurrent ovarian cancer

Drug	Trial	Eligibility	PFS (HR) in BRCAmt	PFS (HR) in BRCAwt
Olaparib	Study019	HGSOC	0.18	0.54
Olaparib	SOLO2	BRCAmt	0.3	-
Niraparib	NOVA	HGSOC	0.27	0.45
Rucaparib	ARIEL3	HGOC	0.23	0.47–0.55

PFS, progression free survival; HR, hazard ratio; BRCA, breast cancer and ovarian cancer related gene; mt, mutant; wt, wild type; HGSOC, high grade serous ovarian cancer; HGOC, high grade ovarian cancer

Table 2. HRR related genes and lifetime risk of cancers

gene	lifetime risk		ref
ATM	Breast	38-69%	(19) (van Os et al. Clin genet2016 p105)
BARD1	Breast	NA	(20) (Kurian AW et al. JCOprescision2017 p1)
BRCA1	Breast	72%	(21) (Kuchenbaecker et al. JAMA2017 p2402)
	Ovarian	44%	
	Prostate	NA	(22) (Liede et al. JCO2004 p735)
	Pancreatic	NA	(23) (Lynch et al. Cancergenet2005 p119)
BRCA2	Breast	69%	(21) Kuchenbaecker et al. JAMA2017 p2402)
	Ovarian	17%	
	Prostate	19%	(24) (Van Asperen et al. JMedgenet2005 p711), (25) (Struewing et al. NEJM1997 p1401)
	Pancreatic	7%	(24) (Van Asperen et al. JMedgenet2005 p711)
BRIP1	Ovarian	5.8%	(26) (Ramus et al.JNCI2015 p107)
CDK12	NA		
CHEK1	NA		
CHEK2	Breast	28-37%	(14) (Cybulski et al. JCO2011 p3747), (15) (Weischer et al. JCO2008 p542)
FAM175A	NA		
FANCA	NA		
FANCD2	NA		
FANCI	NA		
FANCL	NA		
MRE11A	NA		
NBN	NA		
PALB2	Breast	35-58%	(16) (Antoniou et al. NEJM2014 p497)
RAD51	NA		
RAD51C	Ovarian	5.2	(12) (Song et al. JCO2015 p2901)
RAD51D	Ovarian	12	(12) (Song et al. JCO2015 p2901)
RAD52	NA		
RAD54L	NA		
XRCC3	NA		

Table 3. the list of multi-gene panel for cancer clinical sequencing in Japan

Name of panel	PMDA approval	Number of genes†	Germline	Allele frequency‡
NCC Oncopanel	Y	114	Y	Y
FoundationOne	Y	324	N	N
Oncomine	T	46	N	Y
Todai OncoPanel	T	465	Y	Y
OncoPrime	N	233	N	Y
MSK-IMPAKT	N	468	Y	Y

Y, yes; N, No; T, Trial ongoing;

† Number of genes included mutations only.

‡ Shown as 'Y', only if allele frequency officially documented in the report.

efficacy of olaparib. The problem of HRD assays is that negative results do not mean lack of response for the efficacy of PARP inhibitors. In NOVA and ARIEL3, HRD-negative patients also benefit from niraparib (PFS HR = 0.58) or rucaparib (PFS HR = 0.58). Another problem of the HRD assay is lack of consensus regarding the definition of each component, TAI, LOH, and LSTs. Another assay, whole exome sequencing, is a more sensitive method to evaluate HRR. Analyses of tumor-derived genome sequences have shown that loss of *BRCA1* or *BRCA2* yields a distinct pattern of base-substitution mutations, termed Signature 3. This pattern can be discerned via nonnegative matrix factorization, a technique used to identify recurring patterns in the spectra of mutations from a set of tumors and to estimate the contributions of these signatures to the mutational landscape. Analytical validity, clinical validity, and clinical utility of these HRD assays are to be determined in current and future studies. At the moment, these assays failed to beat 'chemo-selection.'

Combination therapy

Because PARP inhibition has immuno-regulatory effects (18), combination therapy of PARP and immune checkpoint inhibitors is being developed. A Phase II study (MEDIOLA) of olaparib and the PD-L1 inhibitor durvalumab in patients with relapsed, platinum-sensitive, *BRCA*-mutated ovarian cancer showed a good objective response rate (ORR) of 72% (n = 23/32) (19) (NCT 02734004). This study expanded the *BRCA*-mutant cohort to 100 patients. In this study, PD-L1 expression and tumor-infiltrating lymphocytes did not associate with clinical outcomes. Then, a phase I/ II study

Table 4a. randomized trials combining PARP inhibitors with immune checkpoint inhibitors

Trial	PARPi	ICI	Setting	BRCA	NCT
Keylink-001	Olaparib	Pembrolizumab	1st line	Wt/Unknown	03740165
ATHENA	Rucaparib	Nivolumab	1st line	Unknown	03522246
FIRST	Niraparib	TSR-042	1st line	Unknown	03602859
JAVELIN-100	Talazoparib	Avelumab	1st line	Unknown	03642132
ANITA	Niraparib	Atezolizumab	PSOC	Mt/Wt	03598270

PARPi, PARP inhibitor; ICI. immune checkpoint inhibitor; BRCA, breast and ovarian cancer gene; Wt, wild type;PSOC, platinum sensitive ovrian cancer; Mt, mutant.

Table 4b. Randomized trials combining PARP inhibitors with anti-angiogenic drugs

Trial	PARPi	Anti-angio	Setting	BRCA	NCT
PAOLA-1	Olaparib	Bevacizumab	1st line	Any	02477644
ICON9	Olaparib	Cediranib	PSOC	Mt/Wt	03278717
GY-004	Olaparib	Cediranib	PSOC	Any	02446600
COCOS	Olaparib	Cediranib	PROC	Any	02502266

PARPi, PARP inhibitor; Anti-angio, antiangiogenic agent; BRCA, breast and ovarian cancer gene; PSOC, platinum sensitive ovrian cancer; Mt, mutant; Wt, wild type; PROC, platinum resistant ovarian cancer.

(TOPACIO) of niraparib and the PD-1 inhibitor pembrolizumab in patients with platinum-resistant/refractory ovarian cancer was performed (20). The ORR was 25% and the disease control rate was 68%. The ORR by biomarkers was 28.5% (n = 2/7) in patients with sBRCAmt, 26.4% (n = 9/34) with sBRCAwt, 26.7% (n = 4/15) with HRD-positive, and 29.2% (n = 7/24) with HRD-negative mutations. There was no difference in response by biomarkers. Currently, several ongoing global phase III studies of PARP inhibitors and immune check point inhibitors (Table 4a).

Because PARP inhibitors and anti-angiogenic inhibitors are also synergistic (21), the combination therapy of PARP inhibitors and anti-angiogenic drugs also has been studied. In a phase II study of olaparib and cediranib for patients with platinum-sensitive recurrent ovarian cancer with or without gBRCAmt, combination therapy significantly improved median PFS compared to olaparib monotherapy (17.7 vs. 9.0 months; HR = 0.42; 95% CI, 0.23–0.76; P = 0.005) (22). The updated analysis was conducted, and median PFS was 8.2 months in the olaparib monotherapy arm and 16.5 months in the olaparib and cediranib arm (HR = 0.42; 95% CI, 0.30–0.83; P = 0.007) (23). In patients known for a gBRCAmt, there was no difference in median PFS (16.5 vs. 16.4 months). On the other hand, in patients without a known gBRCAmt, median PFS in the olaparib and cediranib arm was improved compared to that with olaparib monotherapy (23.7 vs. 5.7 months, HR = 0.32; P = 0.002). There was no OS benefit in all patients, but inpatients without a known gBRCAmt showed a difference of 14 months in OS. Currently, a phase III trial (ICON 9) of maintenance olaparib combined with cediranib compared to olaparib alone in patients with relapsed platinum-sensitive ovarian cancer (NCT03278717) is ongoing. A phase I study of olaparib combined with bevacizumab in patients with advanced solid tumors showed that therapy was well tolerated with no dose-limiting toxicities (24). Currently, a phase III study (PAOLA-1) as maintenance treatment in patients with advanced ovarian cancer following first-line platinum-based chemotherapy plus bevacizumab, comparing bevacizumab plus olaparib with bevacizumab plus placebo, is ongoing (25) (Table 4b).

Moreover, PARP inhibitors combined with immune checkpoint inhibitors and anti-angiogenic drugs are being developed. A Phase III study (DUO-O) on durvalumab combined with chemotherapy and bevacizumab, followed by maintenance durvalumab, bevacizumab, and olaparib is ongoing (NCT03737643).

Future perspectives

All ovarian cancer patients are recommended to have germ line *BRCA* testing according to National Comprehensive Cancer Network guidelines. All breast cancer patients are recommended to undergo germ line panel testing according to American Breast Surgeons Society consensus guidelines, which have been supported by a recent study (26). This trend will increase the number of patients with ovarian cancer who can benefit from PARP inhibitors, with incremental demand for genetic counseling, surveillance, and risk-reducing procedures. Implementation of clinical sequencing also will expand these demands via secondary findings. Education of clinical genetics and co-working with professionals in clinical genetics is urgent needs for gynecologic and medical oncologists in this field.

Supplementary data

Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

Conflict of interest statement

None declared.

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