Title
PARPi after PARPi in epithelial ovarian cancer

Authors
Essel, KG
Behbakht, K
Lai, T
et al.

Publication Date
2021-02-01

DOI
10.1016/j.gore.2021.100699

Peer reviewed

Gynecologic Oncology Reports 35 (2021) 100699

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case series

PARPi after PARPi in epithelial ovarian cancer

K.G. Essel [a,*], K. Behbakht [b], T. Lai [c], L. Hand [d], E. Evans [a], J. Dvorak [a], K. Ding [a], G. Konecny [c], K. N. Moore [e]

[a] University of Oklahoma HSC, Oklahoma City, OK, United States
[b] University of Colorado School of Medicine, Denver, CO, United States
[c] University of California Los Angeles, Los Angeles, CA, United States
[d] University of Pittsburgh, Pittsburgh, PA, United States
[e] The University of Oklahoma, Stephenson Cancer Center, Oklahoma City, OK, United States

ARTICLE INFO

Keywords:
PARP inhibitor
Ovarian cancer

ABSTRACT

The objective of this study was to describe the treatment experience of patients with recurrent epithelial ovarian cancer who are retreated with an inhibitor of poly(ADP-ribose)-polymerase (PARPi). We conducted a multi-institutional, retrospective review of ovarian cancer patients who received ≥2 lines of therapy containing a PARPi. Demographic, clinical, and pathological data were analyzed with descriptive statistics. Twenty-two patients were identified. For initial PARPi (PARPi1), 12 patients (54.5%) received veliparib, 7 (31.8%) olaparib and 3 (13.6%) rucaparib resulting in 10 patients who had no evidence of disease at the completion of therapy (NED), 3 partial responses (PR), 4 stable disease (SD), and 3 progressive disease (PD). (All 10 CRs involved veliparib given in conjunction with cytotoxic chemotherapy). PARPi1 was used as maintenance in 2 patients. PARPi1 was discontinued because planned number of cycles was reached (n = 10), progression (n = 8), toxicity (n = 2), other (n = 2). For second PARPi (PARPi2), 10 patients (45.4%) received niraparib, 6 (27.3%) olaparib, and 6 (27.3%) rucaparib resulting in 3 PR, 13 SD, and 3 PD. PARPi2 was used as maintenance in 3 patients. The 3 patients who experienced a PR to PARPi2 had a BRCA mutation and were NED following PARPi1. PARPi2 was discontinued because of progression (n = 13), toxicity (n = 6), other (n = 2). One patient currently remains on PARPi2. Toxicity after PARPi1 was not associated with toxicity from PARPi2 ($p > 0.05$). With 3 approved PARPi for different indications including frontline and recurrence, the opportunity to reuse PARPi has increased. Characterizing those who should be re-challenged is an important initiative moving forward.

1. Introduction

The landscape for treatment of epithelial ovarian cancer (EOC) is rapidly changing. With the release of data from PAOLA-1, PRIMA, and VELIA exploring the role of PARPi as first-line maintenance, approval has expanded significantly in the last year (Moore, 2018; Coleman, 2019; González-Martín, 2019; Ray-Coquard, 2019). PARPi are now approved for frontline maintenance and for treatment of and maintenance of recurrent EOC.

Many clinical trials excluded patients who had prior exposure to PARPi from participation and as such, patients who participated in early clinical trials of PARPi were not able to participate in more recent trials for recurrent disease. Now that PARPi are approved for a larger number of patients, the opportunity for PARPi use after prior PARPi exposure exists. We have no data regarding the efficacy or safety of repeated use of a PARPi amongst patients who have had exposure to prior a PARPi.

Much like re-use of cytotoxic chemotherapy, there will undoubtedly be determinants of when a PARPi is re-used for a particular patient. These may include time since prior PARPi, response to prior PARPi or progression while receiving prior PARPi, molecular characteristics of the tumor inclusive of *breast cancer gene* (*BRCA*) status or homologous recombination deficient (HRD) status; but may also include other determinants of loss of DNA damage capabilities and perhaps even the ability to test a patient for development of PARPi resistance. In order to evaluate these determinants, clinical trials, such as the OReO (NCT03106987) are critically important to inform efficacy of repeat monotherapy PARPi use. Our study sought to evaluate signals for efficacy in a retrospective, multicenter fashion.

* Corresponding author at: Stephenson Cancer Center at the University of Oklahoma HSC, 800 NE 10th Street, Suite 5050, Oklahoma City, OK 73104, United States.
E-mail address: kessel@tnonc.com (K.G. Essel).

https://doi.org/10.1016/j.gore.2021.100699
Received 5 November 2020; Received in revised form 4 January 2021; Accepted 5 January 2021
Available online 11 January 2021

2. Methods

This was an IRB-approved multi-institutional, retrospective review of patients with EOC who had received ≥2 lines of therapy containing a PARPi at the University of Oklahoma Health Sciences Center, the University of Colorado School of Medicine, the University of California at Los Angeles Medical Center, and Magee-Womens Hospital at the University of Pittsburgh Medical Center.

Twenty-two patients met inclusion criteria. Variables collected included age, details regarding cytoreductive surgery, frontline chemotherapy, first recurrence and treatment, date of initiation of first and second PARPi, date of recurrence following PARPi, best response, dose interruptions, dose modifications, toxicities, vitals status and date of last follow-up. Toxicities were defined and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were defined according to RECIST v1.1 criteria.

Demographic, clinical, and pathological data were summarized descriptively, then analyzed with Fisher's exact test to assess association of toxicity between PARPi1 and PARPi2, association of best response to PARPi1 and PARPi2, and association of *BRCA* status with response to PARPi1 and PARPi2. Additionally, a Cox proportional-hazards model was used to determine whether PFS to PARPi2 was associated with PFS to PARPi1.

3. Results

Twenty-two patients were identified who had prior PARPi exposure and were retreated with a PARPi (Table 1). Median age of diagnosis was 54.5 years. Of these, 11 patients (50.0%) had a germline *BRCA* mutation and 2 patients (9.1%) had a somatic *BRCA* mutation. Twenty patients (90.9%) had high grade serous EOC and 2 patients (9.1%) had mixed EOC (one with mixed high grade serous and high grade endometrioid, and the other with mixed high grade endometrioid and clear cell EOC).

Table 1

Patient Characteristics	n=22
Median age of diagnosis	54.5 years (range, 42-69)
Ethnicity	n (%)
Caucasian	14 (63.6)
Hispanic	3 (13.6)
Native American	1 (4.5)
Asian	1 (4.5)
Unknown/Other	3 (13.6)
BRCA Status	
gBRCA1+	10 (45.5)
gBRCA2+	1 (4.5)
tBRCA1+	1 (4.5)
tBRCA2+	1 (4.5)
All testing neg	9 (40.9)
Stage	
II	2 (9.1)
III	17 (77.3)
IV	3 (13.6)
Cytoreduction	
Primary	20 (90.9)
Interval	1 (4.5)
None	1 (4.5)
Cytoreduction Result	
No Gross Residual	6 (27.3)
<1 cm	11 (50.0)
>1 cm	4 (18.2)
NA	1 (4.5)
Histology	
HG Serous	20 (90.9)
Mixed	2 (9.1)
Maintenance Bevacizumab	12 (54.5)
PARPi	1 (4.5)
None	9 (40.9)
PFI1	15.0 mo (2.0–48.7)

Seventeen (77.3%) were stage III and 20 (90.9%) underwent a primary cytoreductive surgery. All patients received a platinum containing doublet as part of their initial therapy, 12 patients (54.5%) received bevacizumab maintenance following initial chemotherapy and 1 patient (4.5%) received PARPi maintenance. At first recurrence, median platinum free interval was 15.0 months (range, 2.0–48.7 months).

For initial PARPi, most patients received veliparib, followed by olaparib and rucaparib. Nine patients received veliparib in combination with platinum, paclitaxel, and bevacizumab as frontline therapy on GOG9923. Three patients received veliparib in combination with carboplatin, pegylated liposomal doxorubicin hydrochloride, and bevacizumab as treatment for platinum-sensitive recurrence on GOG9927. Six patients received olaparib as treatment in the second-line and beyond, and 1 patient received olaparib as maintenance after receiving frontline platinum-based chemotherapy. Two patients received rucaparib as maintenance after treatment for recurrence, and 1 patient received rucaparib as treatment in the 4th line. For second PARPi, most patients received niraparib followed by olaparib and rucaparib. PARPi1 was discontinued because planned # of cycles was reached (n = 10), progression (n = 8), toxicity (n = 2).

We sought to evaluate if response to PARPi1 correlated with response to PARPi2, however 12 of our patients received veliparib with chemotherapy (but not as maintenance) on a clinical trial which makes it difficult to classify them as responders vs. non-responders. Nevertheless, 10 of those patients were noted to be without evidence of disease (NED) at the end of their therapy. Additionally, 2 patients had received initial PARPi as maintenance, leaving only 8 patients who had received initial PARPi as treatment and for whom response could be assessed. Due to a wide variety of treatment settings in which patients were treated with initial PARPi, it's difficult to classify the "best response" to PARPi1 and consequently to determine if response to PARPi1 predicts response to PARPi2.

While "best response" to PARPi1 was difficult to evaluate, response to PARPi2 was evaluable as treatment settings were more consistent (19/22 patients received PARPi2 as treatment). PARPi2 did not result in any complete responses (CR), however there were 3 patients in whom PARPi2 resulted in a partial response (PR). Those 3 patients all had a *BRCA* mutation and had all been exposed to PARPi1 as part of frontline therapy (Table 2).

Table 2
Treatment data.

	PARPi1	PARPi2
PARPi received	n, (%)	n, (%)
Veliparib	12 (54.5)	0 (0)
Olaparib	7 (31.8)	6 (27.3)
Rucaparib	3 (13.6)	6 (27.3)
Niraparib	0 (0)	10 (45.4)
No. prior regimens, median (range)	1 (0–8)	3.5 (1–10)
Best Response		
NED*	10 (45.4)	0 (0)
Partial Response	3 (13.6)	3 (13.6)
Stable Disease	4 (18.2)	13 (59.1)
Progressive Disease	3 (13.6)	3 (13.6)
Used as maintenance	2 (9.1)	3 (13.6)
Reason for discontinuation of PARPi		
Number of cycles reached	10 (45.5)	0 (0)
Progression	8 (36.4)	13 (59.1)
Toxicity	2 (9.1)	6 (27.3)
Other	2 (9.1)	2 (9.1)
Still on therapy	0 (0)	1 (4.5)
Response of patients w *BRCA* mutation		
NED*	5 (38.5)	0 (0.0)
Partial Response	2 (15.4)	3 (23.1)
Stable Disease	3 (23.1)	8 (61.5)
Progressive Disease	1 (7.7)	2 (15.3)
Used as maintenance	2 (15.3)	0 (0.0)

* All patients who experienced "NED" with PARPi1 received veliparib in conjunction with cytotoxic chemotherapy on either GOG9923 or GOG9927.

When broken down by *BRCA* status, re-treatment with PARPi resulted in 3 PR, 8 stable disease (SD), and 2 progressive disease (PD). There does seem to be a signal for rechallenge with PARPi in this population (Table 2). Three patients received PARPi2 as maintenance. Of those 3 patients, one patient progressed at 3 months, one patient has yet to progress, and the last patient is still on therapy at 24 months.

PARPi2 was discontinued because of PD (n = 13), or toxicity (n = 6). One patient currently remains on therapy with PARPi2 (table 2).

Eight patients discontinued PARPi1 due to progression. Best response: 2PR, 2SD, 3PD, 1 not evaluable as PARPi used as maintenance therapy. Of those pts, best response to PARPi2 was 5 SD and 3PD. Eventually, these patients discontinued PARPi2 due to progression (n = 6) and toxicity (n = 2). Despite the fact that all 8 patients discontinued 1st PARPi due to progression of disease, 5/8 patients may have experienced clinical benefit in the form of SD before progressing. Notably those responses were durable with 3 patients remaining progression free for more than 12 months following initiation of PARPi2 (Table 3).

The most common G3/4 toxicities experienced by patients were hematologic in nature. Toxicity after initial PARPi was not significantly associated with toxicity following second PARPi ($p > 0.05$). There were no occurrences of AML/MDS (Table 4).

Table 4
Toxicities.

	PARPi1	PARPi2
Grade 3/4 anemia	4 (18.2)	1 (4.5)
Grade 3/4 thrombocytopenia	5 (22.7)	5 (22.7)
Grade 3/4 neutropenia	4 (18.2)	1 (4.5)
Grade 3/4 non-hematologic toxicity	3 (13.6)	3 (13.6)
Grade 3/4 any toxicity	10 (45.5)	7 (31.8)

4. Discussion

This is one of the first efforts to report on patients who have been exposed to PARPi in more than one treatment regimen. This is a small study, limited by small numbers and patients receiving first PARPi in a variety of treatment settings. It is difficult to make definitive conclusions other than that patient responses to 2nd PARPi exposure were noted. From this, we conclude prior exposure to PARPi does not necessarily confer resistance to future PARPi and appears to be a safe option in the recurrent setting. Some patients experienced benefit from retreatment with a PARPi, specifically patients with *BRCA* associated tumors whose disease did not progress during PARPi1 as part of frontline therapy. Also, patients who were treated with PARPi1 to progression experienced some clinical benefit in response to PARPi2, which suggests that the development of resistance is not necessarily universal with prior exposure and progression on PARPi. Also, toxicity after initial PARPi was not significantly associated with toxicity following second PARPi. Toxicities were not additive with PARPi2 suggesting that safety may be acceptable.

In September 2019, the results of three major phase III clinical trials demonstrated the benefit of maintenance with PARPi following frontline treatment resulting in FDA approvals (Coleman, 2019; González-Martín, 2019; Ray-Coquard, 2019). Thus, an increasing number of patients are going to be exposed to PARPi in the frontline setting; as the majority of ovarian cancer patients recur, data will be needed on re-treatment efficacy. We need to identify patients who would benefit from re-treatment and to determine if it would be better to utilize monotherapy versus combination therapy in response to acquired PARPi resistance. The question of monotherapy PARPi after PARPi is being investigated in the form of a prospective randomized controlled trial OReO/ENGOT Ov-38 trial (Olaparib retreatment in platinum sensitive recurrent ovarian cancer) (NCT03106987; D0816C00014). This study opened in June 2017 and has an estimated primary completion date of November 2020.

While OReO will answer an important question, others remain including whether we can predict the patients who may benefit from repeat PARPi use and whether we can use combination therapies to overcome acquired platinum resistance. Our current study suggests that patients who did not progress on prior PARPi and, potentially only those with BRCA mutations may benefit from repeat PARPi use; however given the limitations of this study, one cannot make definitive statements. A second, recently presented study did report similar findings. Rimel et al. reported on the 37/463 patients enrolled on the QUADRA study of niraparib in ≥4th line of therapy who had received prior PARPi therapy (Rimel, 2020). Of these, 23 (62%) had a *BRCA* associated EOC, 30 (81%) were HRD+, and 11 (30%) were sensitive to platinum. Thirty-three patients (89.2%) had progressed while on their prior PARPi. The overall response rate (ORR) was 6%; however the clinical benefit rate (CBR) at 16 weeks was 20% indicating some signal of disease control.

Identification of biomarkers for patients who would benefit from PARPi retreatment is currently underway. Pettitt et al. reported on certain point mutations leading to PARPi resistance (Pettitt, 2018). Lin et al have reported on the ability to identify *BRCA* reversion mutations through evaluation of circulating cell free DNA (cfDNA) in both pre and post treatment blood samples from patients being treated with rucaparib (Lin, 2019). From studies of rucaparib where pretreatment biopsies were required, patients with homozygous BRCA1 methylation appeared to benefit from rucaparib therapy and those with heterozygous methylation appeared to be resistant. Loss of homozygosity is likely related to prior exposure to chemotherapy (and potentially PARPi) and may serve as another potential biomarker for sensitivity to PARPi retreatment (Kondrashova, 2018).

In addition to identifying biomarkers, repeat PARPi use may require combination therapies in order to overcome acquired resistance to PARPi. Clinical trials demonstrating benefit of combination PARPi and anti-angiogenesis in BRCAwt EOC have already been reported suggesting that the combinations of PARPi and VEGF inhibitors may overcome inherent PARPi resistance (Liu, 2014; Mirza et al., 2019). In a study by Lheureux et al., 34 patients who had progressed on a prior PARPi were treated with olaparib and cediranib resulting in ORR 12%. This study identified mechanisms of resistance among 19 patients to include *BRCA*1/2 reversion (n = 4), *BRCA*1/2 over-expression (n = 1), multi-drug resistance protein overexpression (n = 2), *CCNE*1 amplification/overexpression (n = 6) and other putative mechanisms (n = 6) (Lheureux et al., 2019). Early phase data demonstrating safety of olaparib and the α specific PI3K inhibitor apelisib also reports a signal for efficacy

Table 3
Patients who received PARPi1 to Progression.

Pt	PARPi1	Best Response	Discontinued for	PARPi2	Best Response	Discontinued for	PFS (months)
1	Veliparib*	PD	Progression	Niraparib	SD	Toxicity	4.93
2	Olaparib	PD	Progression	Rucaparib	SD	Progression	6.03
3	Olaparib	PR	Progression	Rucaparib	PD	Progression	2.43
4	Rucaparib	PR	Progression	Olaparib	SD	Progression	18.30
5	Olaparib	Maint	Progression	Olaparib	SD	Toxicity	13.60
6	Olaparib	SD	Progression	Rucaparib	SD	Progression	16.20
7	Olaparib	SD	Progression	Rucaparib	PD	Progression	4.57
8	Olaparib	PD	Progression	Niraparib	PD	Progression	1.57

* Administered days 1–28 in conjunction with carboplatin and pegylated liposomal doxorubicin on GOG 9927.

(ORR 36%) and has been proposed as a possible combination for PARPi exposed, recurrent EOC (Konstantinopoulos, 2019). Clearly there will have to multiple approaches to combinations based on specific mechanisms of resistance if PARPi are to be used repeatedly.

In summary, this is one of the first studies to report on use of PARPi among patients with recurrent EOC who have prior PARPi exposure. While small and retrospective in nature, it does demonstrate possible efficacy for repeat monotherapy utilization for which confirmation awaits the results of OReO. Importantly, with the increasing use of PARPi in earlier lines of therapy and beyond BRCA associated cancer, an increasing number of patients will be presenting with prior PARPi exposure with/or without progression on PARPi. The ability to use biomarkers to select appropriate therapies and have rational combinations to overcome acquired resistance will be an area of high unmet needs and require continued study.

CRediT authorship contribution statement

K.G. Essel: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing. **K. Behbakht:** Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. **T. Lai:** Data curation, Writing - review & editing. **L. Hand:** Data curation, Writing - review & editing. **E. Evans:** Data curation, Writing - review & editing. **J. Dvorak:** Formal analysis, Writing - review & editing. **K. Ding:** Formal analysis, Writing - review & editing. **G. Konecny:** Data curation, Supervision, Writing - review & editing. **K.N. Moore:** Conceptualization, Methodology, Resources, Supervision, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors wish to report that there is no conflict of interest to disclose with the following exceptions: KG Essel reports that she is a former shareholder of Johnson & Johnson. GE Konecny has served on speakers bureaus for AstraZeneca and Clovis Oncology; has received research funding from Amgen and Merck; and has received honorarium from Novartis. KN Moore reports personal fees and other from Astra Zeneca, grants, personal fees and other from Genentech/Roche, grants, personal fees and other from Immunogen, grants, personal fees and other from Clovis, grants, personal fees and other from Tesaro, personal fees and other from Pfizer, personal fees from Janssen, personal fees from Aravive, personal fees from VBL Therapeutics, personal fees and other from Onco Med, personal fees from Samumed, grants and other from Lilly, personal fees from Eisai, outside the submitted work.

References

Coleman, R.L., et al., 2019. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N. Engl. J. Med. 381 (25), 2403–2415.
González-Martín, A., et al., 2019. Niraparib in patients with newly diagnosed advanced ovarian cancer. N. Engl. J. Med. 381 (25), 2391–2402.
Kondrashova, O., et al., 2018. Methylation of all BRCA1 copies predicts response to the PARP inhibitor rucaparib in ovarian carcinoma. Nat. Commun. 9 (1), 3970.
Konstantinopoulos, P.A., et al., 2019. Olaparib and alpha-specific PI3K inhibitor alpelisib for patients with epithelial ovarian cancer: a dose-escalation and dose-expansion phase 1b trial. Lancet Oncol. 20 (4), 570–580.
Lheureux, S., Oaknin, A., Garg, S., Bruce, J., Dhani, N.C., Madariaga, A., Bonilla, L., Lee, Y.C., Colombo, I., Bhat, G., Bowering, V., White, J., Accardi, S., Tan, S., Braunstein, M., Karakasis, K., Liu, Z., Pugh, T.J., Oza, A.M., 2019. Evolve: A post PARP inhibitor clinical translational Phase II trial of cediranib olaparib in ovarian cancer- A Princess Margaret Consortium- GCIG Phase II Trial. J. Clin. Oncol. Abstract 5521, 37.
Lin, K.K., et al., 2019. BRCA reversion mutations in circulating tumor DNA predict primary and acquired resistance to the PARP inhibitor Rucaparib in high-grade ovarian carcinoma. Cancer Discov 9 (2), 210–219.
Liu, J.F., et al., 2014. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. Lancet Oncol. 15 (11), 1207–1214.
Mirza, M.R., Avail-Lundqvist, E., Birrer, M.J., Christensen, R.D., Nyvang, G.B., Malander, S., Anttila, M., Werner, T.L., Lung, D., Lindahl, G., Hietanen, S., Peen, U., Dimoula, M., Roed, H., Knudsen, A.O., Boufercha, L., Staff, S., Vistisen, A.K., Bjorge, L., Maenpaa, J.U., 2019. Combination of niraparib and bevacizumab versus niraparib alone as treatment of recurrent platinum-sensitive ovarian cancer. A randomized controlled chemotherapy-free study—NSGO-AVANOVA2/ENGOT-OV24. J. Clin. Oncol. Abstract 5505, 37.
Moore, K., et al., 2018. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N. Engl. J. Med.
Pettitt, S.J., et al., 2018. Genome-wide and high-density CRISPR-Cas9 screens identify point mutations in PARP1 causing PARP inhibitor resistance. Nat. Commun. 9 (1), 1849.
Ray-Coquard, I., et al., 2019. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N. Engl. J. Med. 381 (25), 2416–2428.
Rimel, B., et al., 2020. Safety and efficacy results of retreatment with a PARP inhibitor monotherapy in late-line recurrent ovarian cancer: results from a subset of the QUADRA trial. Gynecol. Oncol. 156, e4–e5.