PARPi after PARPi in epithelial ovarian cancer

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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 of frontline and recurrence, the opportunity to reuse PARPi has increased. Characterizing those who should be re-challenged is an important initiative moving forward.

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A B S T R A C T

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.

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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 the 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).

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 1

| Patient Characteristics                  | n = 22 |
|-----------------------------------------|--------|
| Median age of diagnosis                 | 54.5 years (range, 42-69) |
| Ethnicity                               |        |
| 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                                   | 3 (4.5)  |
| None                                    | 9 (40.9) |
| PFSI                                     | 15.0 mo (2.0–48.7) |

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 (15.4) |
| 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.
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 |

1  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 provide possible efficacy for repeat monotherapy utilization for which confirmation awaits the results of ORiO. 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. Behbakhht: 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.

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