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To PARPI or Not to PARPI BRCA Mutated Ovarian Cancer Following First-line Chemotherapy, That is the Question?

Peter G Rose,

Laura M Chambers,

Michelle Kuznicki

Section of Gynecologic Oncology, Women's Health Institute, Cleveland Clinic, Cleveland Ohio, USA

Keywords

Ovarian cancer; BRCA mutation; First-line maintenance PARPi therapy

INTRODUCTION

Although the vast majority of patients with advanced-stage (stages III and IV) ovarian cancer will achieve a clinical complete response to primary treatment, a large percentage of those (approximately 80%) are at risk for recurrence of their ovarian cancer [1]. Currently, two Poly Aadenosine-diphosphate (ADP)-Ribose Polymerase (PARP) inhibitors, olaparib, and niraparib, are approved for advanced-stage maintenance therapy for BRCA mutated ovarian cancer after completion of first-line treatment. Those caring for patients with ovarian cancer know that it is an unpredictable, unkind, and often relentless disease. The quandary faced by oncologists in treating patients with ovarian cancer is analogous to William Shakespeare's Hamlet, "whether it is nobler to suffer the slings and arrows of outrageous fortune Or to take arms against a sea of troubles and by opposing end them"

THE DATA

Multiple randomized trials published in the New England Journal of Medicine over the last 2 years have reported on PARP inhibitors for the management of ovarian cancer in the front-line maintenance setting. Three trials have evaluated front-line PARP inhibitor maintenance as a single agent, SOLO-1, PRIMA, VELIA (2). All three trials showed a Progression-Free Survival (PFS) benefit to PARPi maintenance therapy, with PFS benefit being highest in BRCA mutated and Homologous Recombination Deficient (HRD) tumors.

SOLO-1 was a randomized phase III trial evaluating the efficacy of Olaparib *vs* placebo as maintenance therapy in BRCA positive patients with stage III or IV high grade serous or

Correspondence to: Peter G Rose, Section of Gynecologic Oncology, Women's Health Institute, Cleveland Clinic, Cleveland Ohio, USA; Phone: 001-216-312-5312; rosep@ccf.org.

endometrioid ovarian cancer after partial or complete response to first-line platinum-based therapy [2]. Three hundred and eight-eight patients had germline BRCA mutation and two patients had a somatic BRCA mutation. Patients were randomized 2:1 to Olaparib *vs* placebo for 24 months or until disease progression. The disease-free survival at three years was 60% for Olaparib patients compared to only 27% for placebo (HR 0.3, Cl 0.23–0.41, p<0.001).

PRIMA was a randomized phase III trial evaluating the efficacy of niraparib *vs* placebo as maintenance therapy in patients with stage III or IV ovarian cancer with a response after frontline platinum therapy regardless of their Homologous Recombination Deficiency (HRD) status [3]. Seven hundred and thirty-three patients were randomized in a 2:1 ratio to receive niraparib or placebo for 36 months or until disease progression. While the PFS was significantly improved for all subgroups, the most marked benefit with niraparib compared to placebo was demonstrated for those with BRCA mutated (22.1 *vs* 10.9 months) and HRD positive tumors (19.6 *vs* 8.2 months), compared to patients with HRD negative disease (8.1 *vs* 5.4 months). Overall Survival (OS) at the 24-month interim analysis trended toward niraparib benefit however results are not yet mature (84% *vs* 77%, HR=0.7, 95% CI=0.44–1.11) [3].

In the phase III trial VELIA/GOG-3005 patients with stage III and IV ovarian cancer, regardless of BRCA or HRD status, were randomized (1:1:1) to receive either i) chemotherapy plus veliparib followed by veliparib maintenance, ii) chemotherapy plus veliparib followed by placebo maintenance or iii) chemotherapy plus placebo followed by placebo maintenance [4]. Patients who received veliparib had significantly improved PFS in the intention-to-treat population compared to control (23.5 *vs* 17.3 months, HR=0.68; p<0.001). Notably, improved benefit was found in the BRCA mutation subgroup among patients who received veliparib during chemotherapy and as maintenance compared to the placebo control (34.7 *vs* 22.0 months, HR,=0.44; p<0.001) and the HRD cohort (31.9 *vs* 20.5 months, HR=0.57; p<0.001). In the homologous recombination proficient patients, there was a non-significant benefit 18.2 *vs* 15.1 months for veliparib during chemotherapy and as maintenance (HR 0.81, Cl 0.6–1.09). OS data are still maturing. Patients who received veliparib throughout chemotherapy had a higher incidence of thrombocytopenia, anemia, and nausea [4].

A more recent study PAOLA-l/ENGOT-ov25 evaluated the role of PARP inhibition with bevacizumab *vs* bevacizumab alone as maintenance following first-line chemotherapy [5]. This trial randomized patients with stage III and IV ovarian cancer irrespective of BRCA mutation status following response to platinum-based therapy to maintenance with either olaparib plus bevacizumab or placebo plus bevacizumab, Median PFS was 22.1 months in patients who received combination maintenance with olaparib and bevacizumab compared to 16.6 months with placebo and bevacizumab (HR=0.59; 95% Cl 0.49–0.72; p<0.001). As seen with the other PARPi maintenance studies, the greatest PFS benefit was seen in patients with BRCA mutations or HRD-positive tumors. Those with HRD negative (proficient) tumors did not appear to receive PFS benefit from the addition of olaparib to bevacizumab (HR 1.0,95% Cl 0.75–1.35) [5].

These studies have resulted in a number of FDA approvals for maintenance PARP inhibitors following primary chemotherapy for patients with BRCA mutations. At this point all four trials demonstrated improved PFS but overall survival remains immature. There is currently no data that the use of PARP inhibitors as first-line maintenance therapy will result in improved overall survival or that use of maintenance PARP inhibitor therapy is superior to the use of these agents at the time of recurrence. However, the small nonsignificant survival benefit with olaparib seen in Study 19, which evaluated platinum sensitive recurrent ovarian cancer, improved and became statistically significant only when patients who subsequendy received PARPi were excluded from the data analysis [6]. Additionally, no overall survival benefit was seen in the NOVA trial (niraparib as second-line maintenance) where subsequent PARPi exposure was not controlled [7]. This suggests that subsequent PARPi treatment also improves overall survival.

RISK OF RECURRENCE IN OVARIAN CANCER

The risk of recurrence in ovarian cancer is dependent on the stage at initial presentation with approximately 10%, 30%, and 80% of patients with stage I, II and III/IV recurring, respectively. We previously reported a retrospective analysis of stage III and IV ovarian-peritoneal-tubal carcinoma patients from Gynecologic Oncology Group protocols experienced recurrence following primary cytoreductive surgery and by platinum and taxane-based chemotherapy [1]. Although the focus of this paper was on patients who had the recurrent disease it was noted that 17.5% of the patients who were accrued of these trials did not recur. Other authors have reported long-term survivals for ovarian cancer patients [8].

Younger age, early stage, low grade, and non-serious histology were significant predictors of long-term survival. The improvement in non-serious histologies in their study was related to their earlier stage at diagnosis. However, long-term survival also occurred in women with high-risk ovarian carcinoma. Germline *BRCA* and other homologous DNA repair mutations such as *PALB2, BRIP1, RAD51C*, and *RAD51D* mutations are identified in 20 percent of ovarian carcinoma patients and predict longer progression-free and overall survival [9,10].

As oncologists, we may triage our focus to the sickest patients. While it is nice to see patients who have excellent outcomes following treatment and are in prolonged remission, these tend to not be our main focus. Therefore, a thorough review of BRCA patients is necessary to determine the true risk of recurrence in this population. In a recent review by Soledad et al from the University of Washington regarding their BRCA mutated population 12 of 40 (30%) of patients with BRCA mutations never recurred [11]. At the Cleveland Clinic among 166 FIGO 2014 stage III/IV germ-line BRCA mutated patients followed for greater than 3 years following chemotherapy without PARPi therapy, 31 patients never recurred (median follow-up 8 years, range 3.25–34 years) and an additional 17 patients recurred more than 3 years after their chemotherapy (median 5.1 years, range 3.1–9.5 years) [12]. Collectively, 29% of FIGO 2014 stage III and IV patients without PARPi therapy were disease-free for more than 3 years after completing chemotherapy. Currently, there is no biomarker for recurrence for the patients with BRCA mutations (Table 1).

INDUCTION OF PLATINUM RESISTANCE

Cecare et al. recently published a multicenter Italian retrospective study of BRCA mutated patients receiving olaparib as maintenance therapy following platinum-based chemotherapy [13]. Among 66 patients receiving further treatment after progression following olaparib the response rate was 22.2% 11.1% and 9.5% in patients with platinum-free intervals of >12 months, 6–12 months, and <6 months, respectively. More recently, Baert et al. have reported a poorer response to third-line platinum among BRCA mutated and non-mutated following PARPi exposure, with progressive disease in 40% *vs* 9% [14]. In a recent analysis of BRCA mutated patients in Solo 2 time to the second progression following platinum-based chemotherapy was worse at 7 months *vs* 14 months for the olaparib and placebo-treated groups respectively [15]. In reviewing the response to subsequent platinum-based therapy following PARP inhibitor treatment at the Cleveland Clinic for BRCA mutated patients following PARPi exposure the median PFS to a 2nd or 3rd line platinum was significantly worse than non PARPi exposed at 8.0 months *vs* 19.1 months HR 4.01 (2.25,7.16) p<0.001. Furthermore, among BRCA mutated patients the PFS when subdivided by platinum free interval of 6–12 months, 12–24 months, or greater than 24 months was similar and we found no difference between patients who had BRCA mutations and those who had no BRCA mutations [16].

QUALITY-OF-LIFE

Numerous studies in ovarian cancer have shown the chemotherapy treatment for ovarian cancer is associated with a decreased quality of life. Furthermore, quality-of-life measures significantly improve after chemotherapy has been discontinued. Previously patients with BRCA mutations were likely to achieve a complete response to primary therapy and to begin prolonged remissions. This provided the patient time to be off of chemotherapy with improved quality of life. The current maintenance therapies after first-line therapy result in continuous exposure to agents which are associated with toxicities including nausea, fatigue, and anemia. As demonstrated by the recent paper from the University of Washington, patients with BRCA mutations spend a significant amount of their entire lifetime on treatment [11]. For those with a recurrent disease, it is 54%. The current strategy for immediate maintenance therapy will result in a significantly greater percentage of time spent on treatment with the expected decrease in quality of life. Additionally, as reported at ASCO 2020, 8% of the patients in SOLO 2 who received olaparib developed myelodysplastic syndrome [17]. In patients with BRCA mutations who have the chance to experience a cure or durable remission with platinum-based chemotherapy, the potential to develop a second non-curative malignancy related to maintenance treatment should not be taken lightly. Additional study is necessary to understand the risks of myelodysplastic syndrome in this patient population prior to the universal adoption of PARP inhibitors.

COST

The financial toxicity of maintenance therapy in BRCA mutated ovarian cancer is significant, with an estimated annual cost of approximately $226,000 and $197,000 for olaparib and niraparib, respectively [18].

In summary, while ovarian cancer is a terrible disease, it follows an unpredictable course especially for patients with a known BRCA mutation. Adopting a more conservative treatment approach in this population may avoid overtreatment of up to 35% of patients, allow time off chemotherapy with improved quality of life, avoid inducing platinum resistance early in the course of the patient's disease course, and be cost-conscious in the absence of improved overall survival data. While the recent data using PARP inhibitors in ovarian cancer may be promising, there is still much to be learned about their impact upon survival, response to subsequent therapy, and adverse events with prolonged use, including hematologic malignancies. A randomized trial comparing immediate versus delayed PARP inhibitor maintenance therapy evaluating the efficacy, toxicity, quality-of-life, and cost would be appropriate and informative.

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Table 1

Randomized trials of PARP inhibitors as first-line maintenance in BRCA mutated ovarian cancer.

Trial	Reference	PARPi	Progression-free Survival
SOLO-1	[2]	Olaparib *vs* Placebo	At 3 years 60% *vs* 27% HR 0.3, CI 0.23–0.41, p<0.001
PRIMA	[3]	Niraparib *vs* Placebo	22.1 *vs* 10.9 months HR 0.40 CI 0.27–0.62 p<0.001
VELIA	[4]	Veliparib *vs* Placebo	34.7 *vs* 22.0 months HR=0.44; p<0.001
PAOLA-1	[5]	Olaparib and Bevacizumab *vs* Bevacizumab	37.2 *vs* 21.7 months HR 0.31; 95% CI, 0.20 to 0.47

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