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Experience in the Management of Patients with Advanced or Recurrent BRCA1/2 Mutated Ovarian Cancer with Olaparib at the National Oncology Institute of Panama

Kayra Sanchez Munoz*, Jose Pinto Llerena, Cristiane Martin

Medical Oncology Service, National Oncology Institute of Panama, Panama City, Panama

Email address:

kayra.sanchez@gmail.com (Kayra Sanchez Munoz), josepintollerena@gmail.com (Jose Pinto Llerena), cristi_mp_25@yahoo.com (Cristiane Martin)

*Corresponding author

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Abstract: Introduction: Epithelial ovarian cancer includes high-grade serous histology (HGSOC), which represents 90% of patients and at the time of diagnosis and presents in an advanced stage in 75% of patients. The BRCA1/2 mutation is present in 10-15% of women with this diagnosis. Objective: To describe the clinicopathological characteristics of patients with ovarian cancer with BRCA1/2 mutation and our experience in terms of objective response and survival with the use of olaparib. Methodology: We performed a retrospective review of the electronic records of patients with advanced-stage BRCA 1/2 mutated ovarian cancer or recurrent disease treated with olaparib. Results: 18 patients presented with a BRCA1/2 mutation from 2018 to May 2022, with a mean age of 60 years, and 100% had high-grade serous carcinoma histology. Germline BRCA1 mutations were found in 11 patients and somatic BRCA2 mutations were identified in patients. Fourteen patients were treated in the second line with olaparib, and four were treated in the first line setting. Fifteen patients achieved a partial response to platinum, and the rest had complete responses. With olaparib, the objective response rate was 30%, with the best response being a partial response in six patients (33.3%). The median PFS was 12 months, and the median OS was 29 months in the second line treatment. Conclusions: The incidence of BRCA mutated ovarian cancer appears to be low in patients at our institution; however patients with BRCA1/2 mutation show favorable outcomes following second-line treatment with olaparib. This finding supports a therapy change for patients with this indication to first line olaparib treatment in our institution.

Keywords: Advanced, Ovarian Cancer, BRCA1 and 2, Somatic Mutation, Germline Mutation, Olaparib, Recurrence

1. Introduction

Ovarian cancer is among the most common gynecological cancers, ranking third after cervical and uterine cancer in developing countries and accounting for 3.9% of all diagnosed neoplasms globally [1]. In Panama, according to the Cancer registry of the National Cancer Institute (*Instituto Oncológico Nacional* – ION), ovarian cancer accounts for 3.5% of all cases of cancer diagnosed in 2020 [2], with a mortality rate of 2.9 per 100,000 inhabitants [3].

Epithelial ovarian cancer includes five histological subtypes, of which high-grade serous ovarian carcinoma (HGSOC) accounts for 90% of cases [4]. At the time of diagnosis, 75% patients present with an advanced-stage (III-IV) carcinoma [5].

BRCA1/2 mutations are found in 10-15% of women diagnosed with HGSOC [6], and the BRCA1 and BRCA2 genes are considered tumor suppressor genes because they maintain genomic stability and, therefore, control cell growth [7]. These mutations lead to the loss of proteins related to genome stability and DNA damage repair, particularly those involved in homologous recombination (HR) repair of platinum-generated double-strand breaks, which explains the sensitivity of patients with BRCA mutations to platinum therapy [8].

The combination of chemotherapy with carboplatin and paclitaxel has been the standard of care for HGSOC after

primary cytoreductive surgery [9]. However, new treatments are now available for this pathology, such as poly ADP-ribose inhibitors (olaparib, niraparib, rucaparib). These treatment options interfere with the ability of tumor cells to repair single-stranded DNA damage and are, therefore, effective in a subset of tumors with impaired DNA repair functions [10].

Study 19 was the pivotal study that led to the approval of the first poly (adenosine diphosphate (ADP)-ribose) polymerase (PARP) inhibitor. In this randomized phase 2 trial, olaparib was evaluated as a maintenance therapy in patients with recurrent, platinum-sensitive HGSOC, regardless of BRCA mutation. The results showed a median progression-free survival of 8.4 months in the olaparib arm, in comparison with 4.8 months in the placebo arm (0.35, 95% confidence interval (CI) [hazard ration (HR)]; $p < 0.001$) [11].

In one of the phase 3 trials that evaluated olaparib, the PARP inhibitor used in our institution, as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation (SOLO-2/ ENGOT-Ov21). Notably, in these patients with platinum-sensitive, BRCA-mutated ovarian cancer, recurrence was evaluated. This study showed a significant improvement in the median PFS, which was 19.1 months, in contrast to 5.5 months with the placebo ([HR] 0.30 95% CI (0.22-0.41), $p < 0.001$ [12]. In the subsequent study, OS improved from 38.8 months in the placebo arm to 51.7 months upon long-term treatment with olaparib, with HR=0.74 (95% CI: 0.54-1.00 p=0.0537 [13].

In 2018, olaparib maintenance monotherapy was evaluated in patients with BRCA-mutated ovarian cancer following first-line, platinum-based chemotherapy (SOLO-1). PARP inhibitors were introduced as a first-line treatment after randomizing patients with (germline or somatic) BRCA1- or BRCA2-mutated advanced high-grade serous or endometrioid ovarian cancer who had completed platinum-based chemotherapy. At the three-year follow-up, 60% of patients in the maintenance olaparib group were disease-free, in contrast to only 27% of patients in the placebo arm HR=0.30; (95% CI, 0.23-0.41); $p <0.001$ [14].

In terms of adverse effects, anemia was the most common hematological toxicity among PARP inhibitors, and 85 of 195 (44%) patients treated with olaparib presented with anemia. Gastrointestinal adverse events are common to all PARP inhibitors. Notably, nausea was the most prevalent event, reaching an occurrence of 76% among patients treated with olaparib in this trial. The symptoms were mainly mild, and only 3-4% of patients had grade 3 or 4 nausea. Fatigue has also been reported in 59-69% of patients treated with any of the three approved PARP inhibitors [15].

The main goal of our study was to describe the clinicopathological characteristics of our patients with BRCA 1/2-mutated ovarian cancer and our experience with olaparib as a second-line treatment in terms of objective response and survival.

2. Materials and Methods

2.1. Data Selection

Data on patients with germline or somatic BRCA 1/2-mutated advanced stage or recurrent ovarian cancer treated with olaparib from 2018 to 2022 were collected retrospectively. The data were retrieved from the Oncofarmis electronic records and ION database, with prior consent of the institutional authorities.

2.2. Patient Selection

The following inclusion criteria were used in this study:

1) Patients 18 years of age or older.
2) Diagnosed with recurrent or advanced-stage ovarian cancer.
3) Sensitive to platinum-based chemotherapy.
4) Partial (PR) or complete (CR) response to platinum-based chemotherapy.
5) Germline somatic BRCA 1/2-mutation.

We defined progression-free survival as the time in months between the start of the treatment and disease progression and overall survival as the time in months between the start of the treatment and death or the end of the study.

2.2.1. Patient Follow-Up

The patients were followed up every three weeks with appointments with their treating oncologist, who assessed possible adverse effects of the olaparib treatment. Tomographic studies were performed after every three-to-four treatment cycles. Treatment was continued until progression or poor tolerance to treatment occurred. The use of olaparib was approved by ION in 2018 as a second-line treatment and more recently, in 2021, as a first-line treatment.

2.2.2. Statistical Analysis

Data were collected and analyzed using IBM SPSS Statistics version 26. Patient characteristics were reported using frequency and descriptive statistics. The Kaplan-Meier method was used to analyze progression-free and overall survival.

3. Results

The study sample consisted of 18 patients diagnosed with BRCA1/2-mutated HGSOC undergoing treatment with olaparib from 2018 to May 2022 at the National Cancer Institute of Panama (*Instituto Oncológico Nacional* – INO), with a mean age of 60 years (ranging from 42 to 74). Of these patients, 17 had advanced-stage carcinoma at the time of diagnosis (13 with stage III and 4 with stage IV).

All (100%) of the patients had positive HGSOC histology. In total, four patients received olaparib as a first-line treatment and 18 as a second-line treatment. Both germline and somatic BRCA1/2 sequences were analyzed, and germline BRCA1 mutations were identified in 11 patients (see table 1).

Table 1. *Patient characteristics.*

	N=18	%
Line of tretament		
First Line	4	22%
Second Line	14	78%
Clinical Response after platinum-based therapy		
Complete Response	3	17%
Parcial Response	15	83%
Number of cycles of platinum-based chemotherapy		
0-4 cycles	3	16%
5-6 cycles	10	56%
> 7 cycles	5	28%
ECOG		
0-1	17	94%
>2	1	56%
Histological Type		
High Grade Serous	18	100%
BRCA mutation		
BRCA1	11	61%
BRCA2	7	39%
BRCA mutation Type		
Somatic	7	39%
Germinal	11	61%

3.1. Survival and Response Rate

The objective response rate (PR + CR) was 33.3%, with a clinical benefit (PR+CR+ stable disease (SD)) of 55.5% (Table 3). Disease progression was confirmed in eight patients, of whom one received olaparib as first-line treatment (Table 2).

Table 2. *Olaparib response rate.*

	Frequency n=18 (%)
Partial response	6 (33.3%)
Stable disease	4 (22.2%)
Progression	8 (44.4%)
Objective response rate	6 (33.3%)
Clinical Benefit	10 (55.5%)

The median progression-free survival of our patients was 12 months (95% CI 2.8-21.1), and the median overall survival was 29 months (95% CI 25.07-32.9), among patients who received olaparib as a second-line treatment with a 48-month follow-up (Figure 1 and 2).

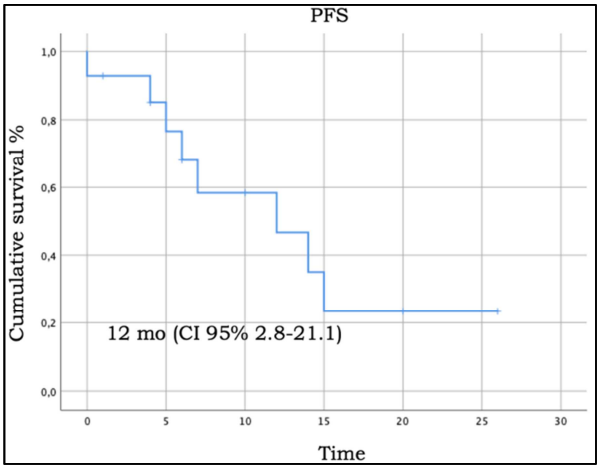

Figure1. *Progression-free survival with olaparib as a second-line treatment.*

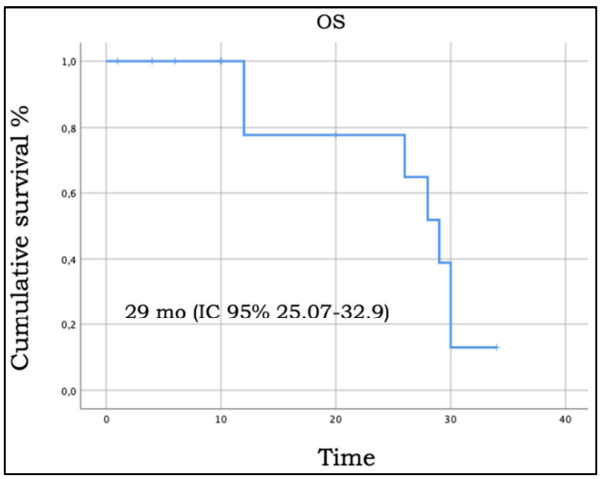

Figure 2. *Overall survival with olaparib as a second-line treatment.*

3.2. Adverse Effects

Adverse events were recorded in 55.5% of patients, and nausea was the most common event. In seven patients with G1-2 adverse events, nausea was followed by fatigue and hyporexia. No G3 gastrointestinal adverse effects were recorded (Table 3).

Table 3. *Adverse Effects.*

Adverse effects	Frequency 10 (55.5%)		
	G1	G2	G3
Hematological			
Neutropenia			1
Thrombocytopenia			1
Gastrointestinal			
Nausea	7	1	
Others			
Fatigue	3	1	
Hyporexia	3		

4. Discussion

This study reports the experience of the ION with olaparib, which was previously approved as a second-line treatment for patients with advanced ovarian cancer. Since 2021, olaparib has been approved as a first-line treatment for these patients. Most epidemiological and pathological characteristics identified in our study are similar to those reported in the literature [5]. The median PFS was 12 months, and the median OS was 29 months, both of which lower than the results from SOLO 2 [12]. Our follow-up period of patients who received olaparib as a second-line treatment was 48 months. The follow-up duration needs to be extended in future studies.

The response rate with Olaparib is 33.3%. In phase 2 trials, the response rates ranged from 30 to 40% [11]. More than 50% of our patients, most of whom presented G1-2 adverse advents, presented particularly with gastrointestinal effects, such as nausea, as previously reported in the literature. Unlike the adverse effects of iPARP, where anemia is the most common G3 adverse event among patients, our patients presented with

neutropenia and thrombocytopenia and did not require treatment discontinuation [15].

Our study has the following limitations. First, this is a retrospective study of a limited number of patients with BRCA1/2 mutations. Nevertheless, our investigation is a hypothesis-generating study.

5. Conclusion

The incidence of BRCA mutated ovarian cancer appears to be low in patients at our institution: however, patients with BRCA1/2 mutation show favorable outcomes following second-line treatment with olaparib. This finding supports a therapy change for patients with this indication to first line olaparib treatment in us institution. The rest of epidemiological and clinical characteristics of our patients are like those reported in the international literature, albeit with lower PFS and OS in this study than in previous studies. The patients who presented with adverse events received medical management, without requiring treatment interruption. We are considering continuing following up these patients and gathering data on our experience with olaparib as a first-line treatment.

Conflicts of Interest

The authors declare that they have no conflicts of interest with respect to this study.

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