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TREATMENT OUTCOMES OF PATIENTS WITH BRCA-MUTATED, RECURRENT OVARIAN CANCER IN UNIVERSITY HOSPITAL CENTER SPLIT

BRANKA PETRIĆ MIŠE[1], MIRKO PEŠO[2], DARIJO HREPIĆ[3], VESNA TELESMANIĆ DOBRIĆ[4] and EDUARD VRDOLJAK[1]

[1]Department of Oncology, University Hospital Split, Split, Croatia;
[2]School of Medicine, University of Split, Split, Croatia;
[3] Department of Medical Psysics, University Hospital Split, Split, Croatia;
[4]Department of Oncology, General Hospital Zadar, Zadar, Croatia

Summary

Aim: To evaluate the treatment outcomes, with emphasis on the efficacy and safety of olaparib, in patients with platinum-sensitive, BRCA-mutated, recurrent ovarian cancer treated at the University Hospital Center Split in the period from June 2016 to April 2021.

Methods: Data were collected retrospectively from a medical history of 28 patients with platinum-sensitive, BRCA-mutated, recurrent ovarian cancer. Medical records were reviewed for clinico-pathological characteristics, number of previous chemotherapy lines and platinum-free interval before olaparib, response to olaparib, survival outcomes (time to disease progression, time from first cycle of olaparib to the first cycle of chemotherapy for the first and second relapse / progression, overall survival) and safety. Median follow up time was 27 months.

Results: All patients were BRCA mutated, with a 75% predominance of BRCA1 mutation. The median platinum-free interval was 13 months. Most patients were treated after the first relapse (64%) with a three-weekly TC protocol (68%). Olaparib maintenance therapy provided clinical control rate in 43% of cases. The median progression free survival was 24 months. Discontinuation of olaparib treatment was reported due to disease progression in 16 patients. The median time to first subsequent chemotherapy was 31 months and time to second subsequent chemotherapy was 38 months. The tolerability of olaparib was good and the side effects were low intensity. The median overall survival is not reached.

Conclusion: This retrospective analysis of patients with platinum-sensitive, BRCA-mutated, recurrent ovarian cancer showed that the treatment outcomes, ie efficacy and tolerability of olaparib after platinum-based chemotherapy in everyday clinical practice, are comparable to those observed in clinical trials with olaparib in the same indications.

KEYWORDS: *ovarian cancer recurrence, BRCA mutation, olaparib, treatment outcomes*

INTRODUCTION

Ovarian cancer is the most lethal gynecological malignancy worldwide. According to global estimates 313959 new cases were detected in 2020, and 207252 women were died from the disease(1). In Croatia, it is the seventh most common cancer among women and the leading cause of gynecological cancer death. The estimated number of new ovarian cancer cases in Croatia in 2018 was 462 with 308 deaths(2).

It is frequently diagnosed at an advanced stage and despite optimal debulking surgery and platinum-based chemotherapy, more than 70% of

***Corresponding author**: Branka Petrić Miše, Department of Oncology, University Hospital Split, Spinčićeva 1, 21000 Split, Croatia and School of Medicine, University of Split, Šoltanska 2, 21000 Split, Croatia, e-mail: brapemi@gmail.com*

patients relapse(3). Recurrent patients can be divided in those that are not candidate to receive a platinum rechallenge (platinum-resistant disease) and those that are candidate to receive platinum again (platinum-sensitive disease)(3,4).

Approximately, 50% of the high-grade ovarian cancer shows an alteration of homologous recombination, that is most important DNA (deoxyribonucleic acid) repair mechanism, active during cell replication(5). Among these alterations, mutations of Breast Cancer 1 and 2 genes (BRCA1/2) are the most important and the most researched so far. Loss of BRCA1/2 function through germline mutation (18%), somatic mutation (6%) or epigenetic silencing lead to homologous recombination deficiency (HRD) and genomic instability, causing a high response rate to platinum-based chemotherapy, increased sensitivity to PARP inhibitors (poly (ADP-ribose) polymerase inhibitors, PARPi) and improved overall survival (OS) compared to BRCA-wild type ovarian cancer patients(5,6).

The activity of PARPi is based on the concept of synthetic lethality, where an underlying homologous recombination deficiency in tumor cells makes the cells highly susceptible to PARP inhibition. PARP inhibitors bind to and trap PARP1 and PARP2 on DNA at the sites of single-strand breaks, which results a double-strand breaks formation. In cancer cells with HRD, double-strand DNA breaks are repaired by error-prone pathways, ultimately leading to cell death(7).

Therefore, PARP inhibitors (i.e. olaparib, niraparib, rucaparib) represent a targeted therapy used for cancer treatment. Olaparib was the first in class drug to be developed and approved in ovarian cancer. Later, niraparib and rucaparib arrived. Despite sharing the same mechanism of action, the toxicity profile is different due to various dose schedule, half-life, drug interactions and metabolism(8). Olaparib is an oral inhibitor of PARP1, PARP2 and PARP3 that has been approved by European Medicines Agency (EMA) in 2014 as maintenance therapy for patients with relapsed, platinum-sensitive, BRCA-mutated, high-grade serous ovarian cancer with complete or partial response to last platinum-based chemotherapy. This approval was based on results from Study 19, a randomized, placebo controlled phase II trial that was confirmed by SOLO2 trial, an international, multicentre, phase III randomized, double blind, placebo controlled trial(9-11). In SOLO2 trial, patients receiving olaparib maintenance therapy achieved an improvement of 13.6 months in progression free survival (19.1 vs 5.5 months in placebo arms, HR 0.30; $P < 0.0001$)(11). In both trials olaparib showed a good safety profile. The most frequent adverse events were nausea, fatigue, vomiting and diarrhea, predominantly low grade(9-11).

The primary purpose of this retrospective study was to analyze treatment outcomes of patients with relapsed, platinum-sensitive, BRCA-mutated ovarian cancers in general clinical practice, with aim to describe the effectiveness and safety of olaparib in real life setting.

PATIENTS AND METHODS

This retrospective study included 28 subjects who have been treated platinum-sensitive, BRCA-mutated, recurrent ovarian, fallopian and peritoneal cancers. All subjects had a germline or somatic mutation of BRCA1/2 genes and achieved a response (complete or partial) to platinum-based chemotherapy. The TC protocol (carboplatin/cisplatin with paclitaxel) was administered intravenously every three weeks or according to the *dose dense* protocol. After last cycle of chemotherapy, olaparib maintenance therapy started at 8-week intervals. The initial formulation of olaparib was a 50 mg capsule that was replaced by 100 mg and 150 mg tablets in 2018, which greatly facilitated the administration of therapy. The daily dose of olaparib from 2016 to 2018 was 800 mg through a capsule formulation (16 capsules of 50 mg per day), and from 2018, tablets in a daily dose of 600 mg were used (4 tablets of 150 mg tablets per day). Patients included in the study received at least one cycle of maintenance therapy with olaparib.

The study was conducted following ethical guidelines of the declaration of Helsinki.

We analyzed the data: date of birth, age at the time of diagnosis, personal and family history related to malignant diseases, primary site of the disease, stage of disease, pathohistological type and grade of the tumor, and BRCA status. Treatment outcomes were investigated by collecting data on the type and response to chemotherapy prior to olaparib therapy: ECOG (Eastern Cooperative Oncology Group) status, number of previ-

ous lines of chemotherapy, ie number of previous relapses, response to chemotherapy and platinum-free interval before olaparib. We analyzed efficacy of olaparib treatment. Disease response to treatment was monitored by the RECIST (Response Evaluation Criteria in Solid Tumors) system. Response to therapy is defined as a complete response (CR) or complete disappearance of the tumor, partial response (Partial Response - PR), stable disease (Stable Disease - SD) or progression of the disease (Progressive Disease - PD). Overall survival (OS) is defined by the period from disease diagnosis to death from a tumor or from some other cause. Progression-free survival (PFS) is defined as the period from the diagnosis of ovarian, fallopian tube, and peritoneal cancer to disease progression, disease recurrence, and/or patient death. TFST (Time to First Subsequent Therapy) is defined as the period from the start of olaparib treatment to the start (chemo)therapy for the first relapse/progression. TSST (Time to Second Subsequent Therapy) is defined as the period from the start of olaparib treatment to the start (chemo)therapy for second relapse/progression. We analyzed tolerability during olaparib treatment. The intensity of treatment side effects was assessed according to CTCAE (Common Terminology Criteria for Advance Events) criteria, v5.0.

Categorical variables were presented as percentages, and a binomial or chi-square test was used to test their differences. Continuous variables were shown as median and interquartile range (IQR). We used Kaplan-Meier method to estimate the median progression free survival, time to first subsequent therapy, time to second subsequent therapy and overall survival with 95% confidence intervals (CI) in the population who received at last one dose of olaparib. We performed the statistical data analysis using GraphPadPrisim 9.1 (GraphPad software, LaJolla, CA, SAD) i Gretl (Baiocchi, Giovanni; Distaso, Walter (2003). *GRETL: Econometric software for the GNU generation*. Journal of Applied Econometrics. 18: 105–110.)

Table 1.

Characteristics of patients before administration olaparib as a maintenance therapy

	n (%)
Age at diagnosis (years), median (range)	55 (36-78)
<50	8 (29)
≥50	20 (71)
Primary tumor location	
Ovarian	20 (71.4)
Fallopian tube	8 (28.6)
Peritoneal	0
Histological type	
Serous	27 (96.4)
Endometrial	1 (3.6)
Grade III	28 (100)
FIGO stage at diagnosis	
I	1 (3.6)
II	2 (7.1)
III	21 (75)
IV	4 (14.3)
BRCA mutation type	
BRCA1 mutation	21 (75)
BRCA2 mutation	7 (25)
Testing for BRCA	
Tumor	2 (7.1)
Blood	26 (92.9)
Positive personal history of breast cancer	5 (17.9)
Positive family history of malignancies	24 (85.7)
Breast cancer in family	16 (66.7)
Ovarian cancer in family	3 (12.5)
Prostate cancer in family	1 (4.2)
Residual disease after primary/interval surgery	
No macroscopic disease	7 (25)
Macroscopic disease	21 (75)

RESULTS

Patients characteristics

Twenty-eight patients with platinum-sensitive, BRCA-mutated, recurrent ovarian, fallopian tube and peritoneal cancers were treated in our institution during a period between June 2016 and April 2021. The median age was 55 years (36-78) with a predominance of those over 50 years. The most often the primary site of disease was ovarian cancer (71%) with serous papillary pathohistological subtype (96%) and grade III (100%). Two thirds of patients were diagnosed at advanced stage (75% patients had FIGO stage III). All pa-

Table 2.
Treatment characteristics before the introduction of olaparib

	n (%)
Time from surgery to olaparib (months), median (range)	36 (16-199)
Chemotherapy lines before	
2	18 (64)
3	5 (18)
4	1 (3.5)
5	4 (14.5)
Chemotherapy protocol before	
TC	19 (67.9)
TC dd	3 (10.7)
TC+bevacizumab	4 (14.3)
Other chemotherapy	2 (7.1)
Response to the chemotherapy before	
Complete response	9 (32)
Partial response	19 (68)
Platina-free interval	
6-12 months	12 (43)
>12 months	16 (57)
ECOG status before	
0	18 (64)
1	10 (36)

TC, paclitaxel, carboplatin; *TC dd*, paclitaxel, carboplatin – dose dense

tients were BRCA mutated. The majority of patients had BRCA1 mutation (75%) detected mainly in the peripheral blood samples (93%). Five patients (18%) treated with olaparib were diagnosed and treated due to metachronic breast cancer. More than half of the patients had a positive family history of breast cancer (57%). In our sample, only 25% of patients after primary cytoreduction were without residual disease. All patients were presented on MDT (Multidisciplinary team) for gynecological cancers to define the optimal treatment strategies. Table 1 shows the patients characteristics before olaparib as a maintenance therapy. Olaparib was started after confirmed response on platinum-based chemotherapy. In our study population, over 50% of patients had platinum-free interval (PFI) longer than 12 months. The median PFI was 13 months. Most patients received olaparib after the first relapse (64%). Two-thirds of patients received a three-weekly TC protocol. One-third of patients had a complete response and the remainder a partial response. Treatment characteristics prior to olaparib administration are listed in Table 2**.**

Table 3.
Olaparib efficacy

	n (%)
Drug formulation	
capsules	13 (46)
tablets	12 (43)
capsules→ tablets	3 (11)
Time from last chemotherapy cycle to first olaparib cycle	
≤ 56 days (8 weeks)	19 (68)
> 56 days	9 (32)
Outcomes to olaparib	
Complete response	3 (11)
Partial response	0
Stable disease	9 (32)
Disease progression	16 (57)
Objective response rate	3 (11)
Clinical control rate	12 (43)

Efficacy of olaparib

The median follow-up was 27 (1.5-52) months. In the follow-up period, 13 patients received olaparib in capsule formulation of 800 mg per day and 12 patients in tablets formulation at a daily dose of 600 mg. In 3 patients, treatment was started with capsules and converted to tablets. Complete regression of the disease was achieved in three patients (11%). One-third of subjects maintained stable disease, including those who started olaparib treatment with a complete response to previous chemotherapy. Clinical control of the disease was achieved in 43% of patients. After 27 months of follow-up, more than 50% of patients progressed. Although the default period from the last cycle of chemotherapy to the first cycle of olaparib was 8 weeks, in 32% of cases it was not followed and treatment was started later. Table 3 shows the treatment outcomes after olaparib as a maintenance therapy.

The median PFS on olaparib therapy was 24 months (2-50). Figure 1 shows the Kaplan - Mayer survival curve of PFS.

Post progression treatment

Discontinuation of olaparib was observed in 16 patients exclusively due to disease progression. The median time from olaparib initiation to chemotherapy initiation for the first relapse (TFST) was 31 months (3-39). Figure 2 shows the Kaplan – Mayer survival curve of TFST.

One patient was lost to follow-up. Fifteen other patients continued treatment according to the protocols of good clinical practice. The most frequent chemotherapy protocol for first relapse after progression to olaparib was the three-weekly TC administered to 11 patients (73.3%). All patients progressed to platinum-based chemotherapy. The median time from olaparib initiation to chemotherapy initiation for the second relapse was 38 months (6-44). Figure 3 shows the Kaplan - Mayer survival curve of TSST.

All patients continued further treatment with sequential chemotherapy. The most common protocol prescribed for the second relapse was etoposide monochemotherapy (53%). Table 4 shows the treatment outcomes after olaparib treatment.

The median OS for our patients was not reached. Figure 4 shows the Kaplan - Mayer OS curve.

Outcomes at the end of follow-up were: 10 patients died due to ovarian cancer (35.7%), 11 patients had relapse and treatment was ongoing (39.3%), and 7 patients were in remission (25%).

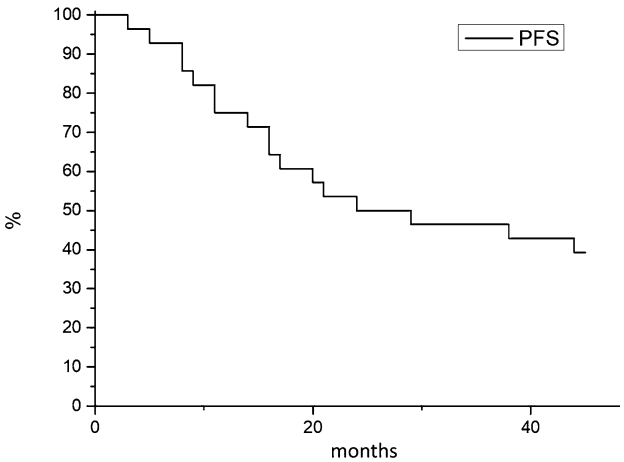

Figure 1. Kaplan-Meier curve of the progression-free survival from the initiation of olaparib (n=28)

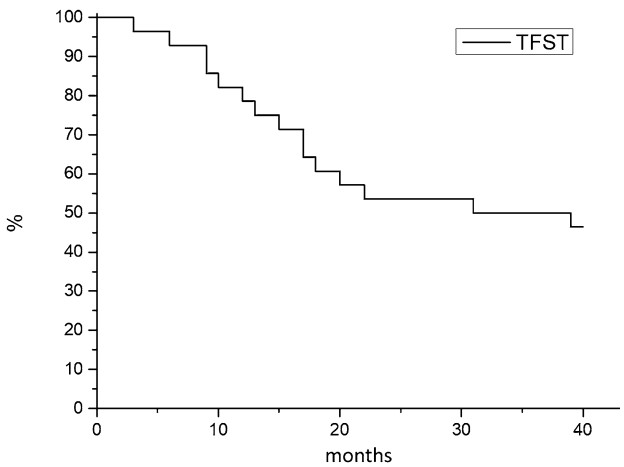

Figure 2. Kaplan-Meier curve of the time of first subsequent therapy (n=15)

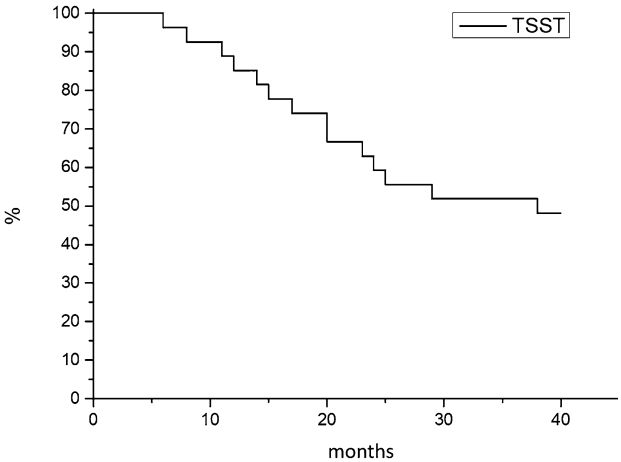

Figure 3. Kaplan-Meier curve of the time to second subsequent therapy (n=15)

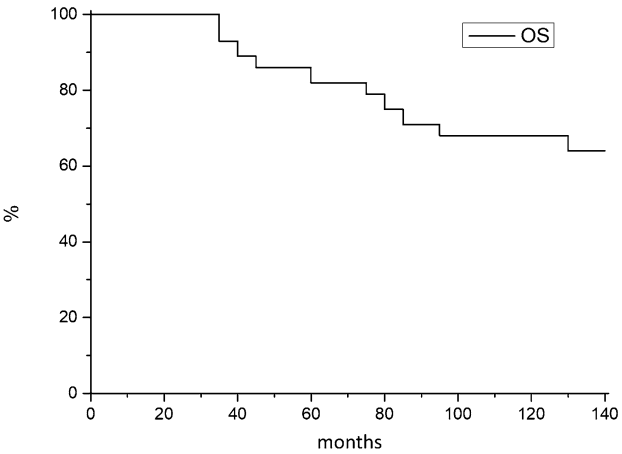

Figure 4. Kaplan-Meier curve of the overall survival from the initiation of olaparib (n=28)

Table 4.

Outcomes after olaparib progression

	n (%)
Time to first subsequent therapy, median (range)	31 (3-39)
Chemotherapy protocol for first ovarian recurrence/progression after olaparib	
TC	11 (73.3)
Carboplatin / cisplatin	2 (13.3)
Ifosfamide	1 (7.7)
Paclitaxel weekly	1 (7.7)
Number of chemotherapy cycles	
≤ 6	10 (66.7)
> 6	5 (3.33)
Response to chemotherapy	
Complete response	0
Partial response	0
Stabile disease	0
Disease progression	15 (100)
Time to second subsequent therapy, median (range)	38 (6-44)

Safety of olaparib

Olaparib treatment was well tolerated. All side effects reported in 75% of subjects were mostly of low grade. The most common non-hematological toxicity was fatigue and nausea with an incidence of 75%. Anemia was reported in a quarter of the patients and thus defined as the most common hematological toxicity. These side effects were treated according to the instructions through drug interruption (8 patients) or by dose reduction (5 patients). None of the subjects discontinued olaparib therapy due to severe toxicity. Tables 5 and 6 show the type and intensity of observed side effects.

Table 5.

Safety outcomes

	Any grade, n (%)	Grade 3 - 4, n (%)
Any toxicity	21 (75)	5 (17.9)
Hematologic toxicity		
Anemia	7 (25)	2 (7.1)
Neutropenia	1 (3.6)	1 (3.6)
Trombocytopenia	0	0
Non-hematologic toxicity		
Fatigue	20 (71.4)	3 (10.7)
Nausea	21 (75)	0
Vomit	1 (3.6)	0
Diarrhea	1 (3.6)	0

Table 6.

Menagement of olaparib toxicity

	n (%)
Dose interruption	8 (28.6)
Dose reduction	5 (17.9)
Discontinuation of treatment	0

DISCUSSION

This retrospective study analyzed 28 patients with BRCA-mutated, recurrent ovarian, fallopian tube, and peritoneal cancers who received olaparib after platinum-based chemotherapy at some point of systemic treatment. We showed that olaparib given in real life setting is active and well tolerated.

PARP inhibitors revolutionized the traditional treatment strategy of ovarian cancer. Olaparib and other PARP inhibitors in maintenance therapy improved PFS in randomized clinical trials phase III in recurrent platinum-sensitive patients treated after response to platinum-based chemotherapy(9-13). Namely, patients receiving olaparib 400 mg twice a day in Study 19, clinical trial phase II, had a longer PFS (8.4 vs 4.8 months in placebo arm, HR 0.35; $P < 0.001$) with a greater benefit in BRCA mutated subgroup (11.2 vs 4.3 months in placebo arm, HR 0.18; $P < 0.0001$)(9,10). These data were later confirmed by the SOLO2 trial, in which BRCA mutated patients receiving olaparib (300 mg tablets, twice daily) had significant benefit in PFS (19.1 vs 5.5 months in placebo arm, HR 0.30; $P < 0.0001$) (11,14). After these results olaparib has been introduced in everyday practice, modifying treatment algorithms. It was approved in the United States in December 2014, first in patients with advanced breast cancer with BRCA mutation. Somewhat later, it was approved in maintenance therapy for recurrent ovarian cancer(15). In Croatia, in 2015, olaparib was approved in maintenance therapy for relapse, and in 2021 in the first-line treatment of ovarian cancer. The initial formulation of olaparib was a 50 mg capsule

that was replaced by 100 mg and 150 mg tablets in 2018, which greatly facilitated the administration of therapy(16).

Results from randomized phase III trials conducted in centers of excellence are often difficult to be repeated in everyday clinical practice. The most important step in evaluating the effectiveness and tolerability of new drugs is their application and analysis in general clinical practice. The added value of such analyzes is carefully monitoring and analyzing the patients and treatments characteristics (demographic characteristics, comorbidity, specificity of mutations for targeted therapy…) that have not been analyzed in clinical studies, but can generate new goals for future research(17).

BRCA mutation is potent target for olaparib. All patients in our study had a proven BRCA mutation, which was mainly detected in the blood sample. The majority of patients (75%) had BRCA1 mutation. This results are consistent with the BRCA status of patients in SOLO2, as well as a number of retrospective reports (11,14,18-28). The specificity of BRCA1/2 carriers is a high risk of breast and ovarian cancer, and a lower risk of pancreatic and prostate cancer(29,30). Breast cancer was diagnosed and treated in five patients (18.5%) in our study population, which is in line with reports from Italian (15.4%) and Korean studies (18%)(19,20). In a multicenter French-Swiss study, 28% of patients had experienced breast cancer(21). A positive family history of breast cancer was higher expressed in our (66%) and Swedish study population (57%) compared to the Italian (42.7%), Chinese (35%) and Korean population (23%) (19,20,22,24).

All patients had platinum-sensitive relapse and confirmed response to platinum-based chemotherapy, which was a prerequisite for olaparib treatment. Olaparib was most commonly administered after the first relapse (64%), which is also consistent with registration studies and real world retrospective reports(9-11,14,18-28). The ratio of complete and partial response as well as the median platinum-free interval was also comparable to registration studies and retrospective reports (9-11,18-28) which indicates that population selection is so important and can ensure the same efficacy of the drug in everyday clinical practice like in randomized clinical study.

Although 8 weeks was considered sufficient for recovery from chemotherapy and delivery of olaparib, 9 patients (32%) started treatment after 8 weeks of the last cycle of chemotherapy. None of the retrospective reports observed the time interval from last chemotherapy to olaparib initiation (18-28).

The efficacy of olaparib was defined through response rate, PFS and OS. Studies have reported experiences with olaparib after different lengths of follow-up, so the proportion of those with a complete and partial response as well as the median PFS and OS are different(15).

After a median follow-up of 27 months, only 11% (3 patients) responded to olaparib, 32% (9 patients) had stable disease, including those who started olaparib without measurable disease, and 57% (16 patients) was progressed. These data are completely consistent to Croatian study, where median follow-up was 16 months(18). Patients in the SOLO2 study had a higher response rate expressed through an objective rate of 41%(11,14). In an Italian study 39% of patients achieved a complete response and 45% a partial response, after median follow-up of 15.5 months(19). In a Chinese study involving 28 patients, only 2 patients had a complete response and 3 patients a stable disease(22). In a study by Labidi-Galy et al. with 114 patients, a complete response was achieved in 33% of subjects and a partial response in 53% of subjects(21). In a Korean study that included 100 patients after a median follow-up of 10.3 months, the complete response rate was 22.6%(20). The lower rate of complete response to olaparib could be explained by the small number of patients in the study and the fact that one third of patients were treated with olaparib after the second relapse. Four patients (14.5%) received olaparib after 5 lines of chemotherapy, compared with 4% in the SOLO2 and Korean study and 11% in the Italian study(11,19,20).

Median progression free survival was 24 months, which is slightly longer compared to retrospective real world data where the median PFS was ranged between 12.7 and 21 months, as well as a multicenter, placebo-controlled phase III clinical study (19.1 month)(11,14,18-28).

Maintenance therapy with olaparib in ovarian cancer population delayed the relapse or disease progression, ie the initiation of chemotherapy

and provided a better quality of life. Novel intermediate endpoints between PFS and OS, TFST and TSST, have been included in ovarian cancer clinical trials. Interestingy, we repeated results from Italian study and SOLO2 where patients progressing to olaparib and treating mostly with platinum–based chemotherapy had a poor response rate and short time to further progression(19,31). In our study, median TFST was 31 months with 86% reintroduction of platinum-based chemotherapy. Unfortunately, all treated patients progressed. The median TSST was 38 months and most of patients were treated with monochemotherapy, mainly etoposide. In Study 19, TFST and TSST were significantly longer in olaparib arm than in placebo arm (TFST 15.6 vs 6.2 months, HR 0.33; P < 0.00001; TSST 21.4 vs 15.3 months, HR 0.43; P < 0.00001) (7). In ESMO meeting 2020 presented the results of secondary analysis of post-progression outcomes in SOLO2 study through a median TFST (27.4 months) and a median TSST (35.8 months)(31). With major limitations due to the unbalance between the two treatments arms at olaparib/placebo progression, patients in the placebo arm seemed to benefit the most from rechallenge with platinum, while those who received olaparib did worse. At the time of report, from 295 included patients, 186 progressed in the olaparib arm and 161 in the placebo arm. From at all progressive patients, 147 received chemotherapy (96 platinum-based and 51 non-platinum-based chemotherapy). For the group of patients treated with platinum-based chemotherapy, the median time to next progression was 14.3 months if they had previously received placebo versus 7 months if treated with olaparib. For non-platinum chemotherapy, the difference was minimal (8.3 versus 6 months). This post-hoc analysis suggests that platinum-based chemotherapy is not the treatment of choice after progression to olaparib(31). These findings are in accordance with a MITO retrospective study of 234 patients with BRCA1/2 mutated recurrent ovarian cancer receiving olaparib as for clinical practice. The study found a lower than expected response rate to subsequent platinum therapy that, in patients with a PFI more than 12 months at the time of recurrence to olaparib was only about 22%(19). A similar finding has been presented by Baert et al. in a mixed population of patients treated with olaparib and niraparib, who showed a low response rate to subsequent platinum chemotherapy compared to the PARPi naive population(32). Own clinical experience and initial observations suggest that BRCA mutated tumors progressing during PARP inhibitors may have cross-resistance to platinum. The molecular drivers of resistance to PARPi are not fully known, but are thought to involve the restoration of homologous recombination proficiency through reverse mutation in BRCA1, RAD51C, and RAD51D, demethylation of the BRCA1 promotor and overexpression of the ABCB1, which encodes a transmembrane drug exporter. PARPi and platinum agents share several mechanisms of resistance that can explain the cross-resistance to the two drugs(33). This experience from everyday clinical practice is extremely important as we still do not have guidelines about chemotherapy sequencing after progression to olaparib.

The median OS in our study was not reached. At the end of the follow-up period (April 1, 2021), we found that 10 patients died of ovarian cancer (35.7%), 11 patients had relapsed treatment (39.3%), and 7 patients were in remission (25%). To date, retrospective reports with different median of follow-up period have defined a median OS ranging from 20.4 to 35.4 months(10,14,19, 21,24,28). A recent SOLO2 study report with a median follow-up of 65 months showed that olaparib versus placebo prolonged overall survival by 12.9 months (51.7 versus 38.8 months)(34).

Our study confirmed a good and acceptable side effect profile of olaparib. The majority of patients (75%) had one or more adverse events, most of which were grade 1 or 2. The most common non-hematological toxicity was fatigue and nausea with an incidence of 75%. The results are consistent with the results of study 19, SOLO 2, and the Chinese study(9,10,11,14,22). However, a Slovenian and Korean studies reported a low incidence of nausea and vomiting (13%) and fatigue (6%)(20). Anemia was the most hematological toxicity. It was reported in 25% of the patients. Severe hematological toxicity, ie. anemia grade 3 and 4 was observed in 7% of patients, which is consistent with the report of Study 19 (5%), Slovenian (10%), Chinese (10.7%) and Korean study (10%), but much lower compared to the results SOLO2 study (19%)(9,10,11,14,21,22). These side effects were treated according to the instructions through dose interruption, in 8 patients (29%) or dose reduction, in 5 patients (18%), which are consistent

with an Italian study where 21% of patients were treated with a reduced dose(19). Compared with the SOLO2 study, we had low drug interruption (45%) and a low dose reduction (25%)(14). None of our patients discontinued olaparib therapy due to severe toxicity. Permanent discontinuation of treatment recorded in 11% of cases in the SOLO2 study, 12.5% in the Royal Marsden hospital, 4.7% in the Italian study, and 3.3% in a large multicenter Chinese study where olaparib was tested in first-line treatment and relapse(14,19,22,26).

The main limitations of this study are the retrospective design, the small number of patients and relatively short overall follow-up period from the initiation of olaparib. However, the value of this report is contained in the analysis of data from everyday clinical practice through multi-year follow-up of patients with recurrent BRCA-mutated ovarian cancer.

CONCLUSION

We showed that olaparib given in real life setting is active and well tolerated. In this retrospective analysis, olaparib in the maintenance setting in relapsed BRCA-mutated ovarian cancer showed long PFS and OS, similar to those observed in Study 19, SOLO2 and real world data from other institutions. Data on post-progression treatments seem to suggest cross resistance with chemotherapy and need to be confirmed in larger studies because of the potential importance for clinical practice decisions.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249. doi: 10.3322/caac.21660.
2. https://www.hzjz.hr/wp-content/uploads/2018/Bilten-2018_završna.pdf Accessed on 30th November 2021
3. Colombo N, Sessa C, du Bois A, Ledermann JA, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumors and recurrent disease. Ann Oncol. 2019;30:672-705. doi: 10.1093/annonc/mdz062
4. Buechel M, Herzog TJ, Westin SN, Coleman RL, Monk BJ, Moore KN. Treatment of patients with recurrent epithelial ovarian cancer for whom platinum is still an option. Ann Oncol. 2019;30:721-732. doi: 10.1093/annonc/mdz104.
5. da Costa AABA, Canto MO, Larsen SJ, Ribeiro ARG, Stecca CE, Petersen AH et al. Genomic profiling in ovarian cancer retreated with platinum based chemotherapy presented homologous recombination deficiency and copy number imbalances of CCNE1 and RB1 genes. BMC Cancer. 2019;19:422. doi: 10.1186/s12885-019-5622-4
6. Pennington KP, Walsh T, Harrell MI, Lee MK, Pennil CC, Rendi MH, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin Cancer Res. 2014;20:764-775. doi: 10.1158/1078-0432.CCR-13-2287
7. Ledermann JA, Pujade-Lauraine E. Olaparib as maintenance treatment for patients with platinum-sensitive relapsed ovarian cancer. Ther Adv Med Oncol. 2019;11:1-18. doi: 10.1177/1758835919849753
8. Valabrega G, Scotto G, Tuninetti V, Pani A, Scaglione F. Differences in PARP inhibitors for the treatment of ovarian cancer: Mehanisms of action, pharmacology, safety and efficacy. Int J Mol Sci. 2021;22:4203. doi: 10.3390/ijms22084203
9. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366:1382-1392. doi: 10.1056/NEJMoa1105535
10. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol. 2014;15:852-61. doi: 1016/S1470-2045(14)70228-1
11. Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18:1274-84. doi: 10.1016/S1470-2045(17)30469-2
12. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med. 2016;375:2154-64. doi: 10.1056/NEJMoa1611310
13. Ledermann JA, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A et al. Rucaparib for patients with platinum-sensitive, recurrent ovarian carcinoma (ARIEL-3): post-progression outcomes and updated safety results from randomized placeo-controlled phase 3 trial. Lancet Oncol. 2020;21:710-22. doi: 10.1016/s1470-2045(20)30061-9
14. Penson R, Kaminsky-Forrett M, Lederman JN, Brown C, Plante M, Korach J, et al. Efficacy of olaparib main-

tenance therapy in patients with platinum-sensitive relapsed ovarian cancer by number of lines of prior chemotherapy: phase III SOLO2 trial (ENGOT Ov-21). Ann Oncol. 2017:350-354. doi: 10.1093/annonc/mdx 372.002

15. Borrelli EP, McGladrigan CG. Real-world evidence of poly ADP-ribose polymerase inhibitors in the treatment of ovarian cancer: A systematic literature review. J Oncol Pharm Pract. 2020;26:1977-86. doi: 10.1177/ 1078155220940043
16. Mateo J, Moreno V, Gupta A, Kaye SB, Dean E, Middleton MR et al. An adaptive study to dermine the optimal dose of the tablet formulation of the PARP inhibitor olaparib. Target Oncol. 2016;11:401-15. doi: 10.1007/s11523-016-0435-8
17. D Sargent. What constitutes reasonable evidence of efficacy and effectiveness to guide oncology treatment decisions? The Oncologist 2010;15:19-23. doi: 10.1634/ theoncologist.2010-S1-19
18. Majić A, Petrić Miše B, Matković V, Belac Lovasić I, Katić K, Canjko I et al. Olaparib outcomes in patients with BRCA 1-2 mutated, platinum-sensitive, recurrent ovarian cancer in Croatia: A retrospective Nonintervantional Study. J Oncol. 2020. doi: 10.1155/2020/ 6423936.
19. Cecere SC, Giannone G, Salutari V, Arenare L, Lorusso D, Ronzino G et al. Olaparib as maintenance therapy in patients with BRCA 1-2 mutated recurrent platinum sensitive ovarian cancer: Real world data and post progression outcome. Gynecol Oncol. 2020;156:38-44. doi: 10.1016/j.ygyno.2019.10.023.
20. Paik ES, Lee YJ, Lee JY, Shin W, Park SY, Kim SI et al. Real-world experience of olaparib maintenance in high-grade serous recurrent ovarian cancer patients with BRCA1/2 mutation: a Korean multicenter study. J Clin Med. 2019;8:1920. doi: 10.3390/jcm8111920
21. Labidi-Galy SI, de La Motte Rouge T, Derbel O, Wolfer A, Kalbacher E, Olivier T et al. Clinical factors associated with prolonged response and survival under olaparib as maintenance therapy in BRCA mutated ovarian cancers. Gynecol Oncol. 2019;155:262-69. doi: 10.1016/j.ygyno.2019.09.008
22. Ni J, Cheng X, Zhou R, Xu X, Guo W, Chen X. Olaparib in the therapy of advanced ovarian cancer: first real world experiences in safety and efficacy from China. J Ovarian Res. 2019;12:177. doi:10.1186/s13048-019-0594-1
23. Blecharz P, Madry R. EP803 The real-world effect of olaparib in BRCA-dependent platinum-sensitive recurrent ovarian cancer patients in Poland. Int J Gynecol Cancer. 2019;29:A443. doi: 10.1136/ijgc-2019-ESGO.853
24. Eriksson I, Wettermark B, Bergfeldt K. Real-world use and outcomes of olaparib: a population-based cohort study. Target Oncol. 2018;13:725-33. doi: 10.1007/ s11523-018-0604-z
25. Rouge TD, Pautier P, Alexandre J, Ray-Coquard I, Cottu P, Rodrigues M et al. First real life data on olaparib in BRCA1/2 mutated platinum-sensitive relapsed (PSR) epithelial ovarian cancer (EOC) in France: analysis of 52 patients (PTS) enrolled in the French Temporary Authorization for Use (ATU). Eur J Cancer. 2015; 51:S548-49. doi: 10.1016/2FS0959-8049(16)31521-0
26. Orbegoso Aguilar CMA, Dumas L, Davies E, Gore M, George A, Banerjee S. Olaparib maintenance treatment, the Royal Marsden experience. Ann Oncol. 2018;29(9):ix84 (abst273P)
27. Zheng H, Gao Y, Guo H, Li L, Li Q, Cui H et al. Real-world experience of olaparib treatment in patients with ovarian cancer: a chinese multicenter study. Mol Cancer Ther. 2021;20:1735-42. doi: 10.1158/1535-7163. MCT-20-1064
28. Gregorič B, Škof E. Olaparib single - centre experience in relapsed epithelial ovarian cancer in Slovenia. Int J Gynecol Cancer 2020;30(Suppl3):A53-A54. doi: 10. 1136/ijgc-2020-IGCS.100
29. Kuchenbaecker K, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ et al. Risks of breast, ovarian and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 2017;317(23):2402-2416. doi: 10.1001/jama.2017.7112
30. Pilarski R. The role of BRCA testing in hereditary pancreatic and prostate cancer families. ASCO Educational book 2019,79-86. doi: 10.1200/EDBK_ 238977
31. Frenel J, Kim J, Berton-Rigaud D, Asher R, Vidal L, Pautier P et al. Efficacy of subsequent chemotherapy for patients with BRCA1/2 mutated platinum-sensitive recurrent epithelial ovarian cancer (EOC) progressing on olaparib vs placebo: The SOLO2/ENGOT Ov-21 trial. Ann Oncol. 2020;31:S615. doi: 10.1016/j. annonc.2020.08.952
32. Baert T, Ataseven B, Bommert M, Concin N, Frindte J, Schneider S et al. 828P Expected versus observed response to platinum-based chemotherapy after poly (ADP-ribose) polymerase inhibitor treatment for relapsed ovarian cancer. Ann Oncol. 2020;31:S624. doi: 10.1016/j.annonc.2020.08.967
33. McMullen M, Karakasis K, Madariaga A, Oza AM. Overcoming platinum and PARP-inhibitor resistance in ovarian cancer. Cancers 2020;12(6):1607. doi: 10. 3390/cancers12061607
34. Poveda A, Floquet A, Ledermann JA, Asher R, Penson RT, Oza AM et al. Final overall survival (OS) results from SOLO2/ENGOT-ov21: A phase III trial assessing maintenance olaparib in patients (pts) with platinum-sensitive, relapsed ovarian cancer and a BRCA mutation. J Clin Oncol. 2020;38(15):6002. doi: 10.1200/ JCO.2020.38.15_suppl.6002

Sažetak

ISHODI LIJEČENJA BOLESNICA S BRCA MUTIRANIM RECIDIVOM KARCINOMA JAJNIKA U KLINIČKOM BOLNIČKOM CENTRU SPLIT

B. Petrić Miše, M. Pešo, D. Hrepić, V. Telesmanić Dobrić, E.Vrdoljak

Cilj: Ispitati ishode liječenja, s naglaskom na učinkovitost i sigurnost olapariba, kod ispitanica s platina-osjetljivim, BRCA mutiranim recidivom karcinoma jajnika liječenih u Kliničkom bolničkom centru Split u razdoblju od lipnja 2016. do travnja 2021. godine.

Metode: Retrospektivno su prikupljeni podatci iz povijesti bolesti 28 bolesnica s platina-osjetljivim, BRCA mutiranim recidivom karcinoma jajnika. Iz medicinske dokumentacije pregledane su kliničko-patološke karakteristike, broj prethodnih linija kemoterapije i interval bez platine prije olapariba, odgovor na olaparib, ishodi preživljavanja (preživljenje do progresije bolesti, preživljenje od prvog ciklusa olapariba do prvog ciklusa kemoterapije za prvi i drugi recidiv/progresiju, ukupno preživljenje) i podnošljivost liječenja olaparibom. Medijan praćenja bio je 27 mjeseci.

Rezultati: Sve bolesnice su bile BRCA mutirane, sa 75% prevlasti BRCA1 mutacije. Medijan platina-slobodnog intervala iznosio je 13 mjeseci. Većina bolesnica liječena je nakon prvog relapsa (64%) trotjednim TC protokolom (68%). Terapija održavanja olaparibom osigurala je kliničku kontrolu bolesti u 43% slučajeva. Medijan preživljavanja bez progresije bio je 24 mjeseca. Prekid liječenja olaparibom prijavljen je zbog progresije bolesti u 16 bolesnica. Medijan vremena do prve sljedeće kemoterapije bio je 31 mjesec, a do druge sljedeće kemoterapije bilo je 38 mjeseci. Podnošljivost olapariba bila je dobra, a nuspojave slabog intenziteta. Medijan ukupnog preživljenja nije postignut.

Zaključak: Ova retrospektivna analiza liječenja bolesnica s platina-osjetljivim, BRCA mutiranim recidivom karcinoma jajnika je pokazala da su ishodi liječenja, odnosno učinkovitost i podnošljivost olapariba nakon kemoterapije temeljene na platini u svakodnevnoj kliničkoj praksi, usporedivi s rezultatima kliničkih istraživanja s olaparibom u istoj indikaciji.

KLJUČNE RIJEČI: *recidiv karcinoma jajnika, BRCA mutacije, olaparib, ishodi liječenja*