Efficacy of PARPi monotherapy and the impact to subsequent platinum-based chemotherapy in BRCA1/2 mutant ovarian cancer patients with secondary platinum-sensitive relapse

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Abstract

Objective: The therapeutic effect of PARP inhibitors (PARPi) monotherapy compared with platinum-based chemotherapy, and the impact to subsequent platinum-based chemotherapy after PARPi resistance were inconclusive. Design: Retrospective cohort study. Setting: Patients from seven medical centers in China. Population: BRCA1/2-mutated ovarian cancer patients with secondary platinum-sensitive relapse, without any maintenance regimen after first- and second-line platinum therapy, and the secondary platinum-free interval (PFI) was more than 6 months. Methods: Patients in study group (n=31) were treated with PARPi monotherapy until disease progression, and patients in control group (n=33) were treated with platinum-based chemotherapy without restriction. Main Outcome Measures: RECIST and GCIG standard, Kaplan-Meier plotter Results: The objective response rate (ORR: 77.4% vs. 84.0%, p=0.538) and median progression-free survival (mPFS: 8.6 vs. 11.1 months, p=0.679) were comparable. PARPi monotherapy significantly prolonged post-recurrent survival (PRS, HR=0.35, p=0.024), and was the independent factor associated with PRS (HR=0.33, p=0.038). The median time from treatment to first subsequent therapy or death (TFST) of patients with platinum-based chemotherapy after PARPi progression and patients in control group with PFI[?]6months after third-line platinum-based chemotherapy was comparable (mTFST: 7.5 vs. 7.1 months, p=0.800). Further survival analysis showed that PRS of patients with PARPi monotherapy were similar to patients with PFI[?]6 months after third-line platinum chemotherapy (HR=0.66, p=0.503), and superior to patients with PFI<6 months after third-line platinum chemotherapy (HR=0.15, p=0.009). Conclusions: PARPi monotherapy was equivalent to platinum-based chemotherapy for BRCA1/2-mutated ovarian cancer patients with secondary platinum-sensitive recurrence, and could improve prognosis.

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Abstract

Objective: The therapeutic effect of PARP inhibitors (PARPi) monotherapy compared with platinum-based chemotherapy, and the impact to subsequent platinum-based chemotherapy after PARPi resistance were inconclusive.

Design: Retrospective cohort study.

Setting: Patients from seven medical centers in China.

Population: BRCA1/2-mutated ovarian cancer patients with secondary platinum-sensitive relapse, without any maintenance regimen after first- and second-line platinum therapy, and the secondary platinum-free interval (PFI) was more than 6 months.

Methods: Patients in study group (n=31) were treated with PARPi monotherapy until disease progression, and patients in control group (n=33) were treated with platinum-based chemotherapy without restriction.

Main Outcome Measures: RECIST and GCIG standard, Kaplan-Meier plotter

Results: The objective response rate (ORR: 77.4% vs. 84.0%, p=0.538) and median progression-free survival (mPFS: 8.6 vs. 11.1 months, p=0.679) were comparable. PARPi monotherapy significantly prolonged post-recurrent survival (PRS, HR=0.35, p=0.024), and was the independent factor associated with PRS (HR=0.33, p=0.038). The median time from treatment to first subsequent therapy or death (TFST) of patients with platinum-based chemotherapy after PARPi progression and patients in control group with PFI[?]6months after third-line platinum-based chemotherapy was comparable (mTFST: 7.5 vs. 7.1 months, p=0.800). Further survival analysis showed that PRS of patients with PARPi monotherapy were similar to patients with PFI[?]6 months after third-line platinum chemotherapy (HR=0.66, p=0.503), and superior to patients with PFI<6 months after third-line platinum chemotherapy (HR=0.15, p=0.009).

Conclusions: PARPi monotherapy was equivalent to platinum-based chemotherapy for BRCA1/2-mutated ovarian cancer patients with secondary platinum-sensitive recurrence, and could improve prognosis.

Key words: PARPi monotherapy, platinum-sensitive recurrence, BRCA1/2 mutation, post-recurrent survival

Tweetable abstract

PARPi monotherapy was equivalent to platinum-based chemotherapy for BRCA1/2-mutated patients, and could improve prognosis.

Background

Ovarian cancer is a common malignant tumor of female reproductive system and its mortality ranks first among gynecological malignant tumors[1]. Although surgical techniques have improved and the vast majority of patients are sensitive to paclitaxel combined with platinum-based chemotherapy, more than 75% of patients eventually relapse within two years of initial treatment[2]. Patients with platinum-sensitive relapse are recommended re-challenge with platinum-based chemotherapy until platinum resistance, however, once platinum resistance occurs, the response rate of subsequent chemotherapy is only about 10-25%, and the prognosis is extremely poor, with median survival of only 12 months[2, 3].

Breast cancer susceptibility genes (BRCA) participate in the repair of DNA double-strand breaks through homologous recombination (HR). BRCA1/2 mutant ovarian cancer cells have impaired repair of DNA double-strand breaks, so the DNA repair pathway relies on poly (ADP-Ribose) polymerase (PARP) to mediate repair of DNA single-strand breaks to maintain DNA survival[4]. Therefore, PARP inhibitors can block the repair of DNA damage in BRCA mutant cells and lead to cell apoptosis, which is known as the "synthetic lethal" effect[4]. Conventional platinum-based therapy follows a frequent relapse-response pattern, so subsequent chemotherapy response and prognosis can be predicted based on the patient's platinum-free interval[5], however, the regimen of PARPi is different and continuous treatment is recommended until disease progression[6, 7], so the concept of PFI has become controversial. The sensitivity of platinum drugs is highly consistent with the response of PARPi, as both are closely related to alterations in DNA damage repair, which also leads to significant overlap between platinum and PARPi resistance mechanisms[8].

Several PARPi are currently available for the clinical treatment of patients with ovarian cancer, and can significantly improve PFS[6, 9], however, there was no relevant study on whether PARPi monotherapy was more beneficial compared with platinum-based chemotherapy. Besides, several clinical data suggested that prolonging the PFI (using non-platinum-based regimens) might restore platinum sensitivity and thus improved survival[10, 11], thus, as a non-platinum-based treatment regimen, PARPi monotherapy after relapse could prolong the PFI, but it was unknown whether platinum-based chemotherapy was more effective after PARPi resistance, and whether it could prolong the survival of patients. Therefore, we conducted this retrospective analysis to try to address this clinically urgent question.

Methods

Patients and clinical data

The flow chart of the study population was shown in Figure 1.Patients included in this study were diagnosed in Qilu Hospital of Shandong University, Cancer Hospital of Beijing Academy of Medical Sciences, Cancer Hospital affiliated to Sun Yat-sen University, Shanghai General Hospital, Fudan University Shanghai Cancer Center, Shandong Cancer Hospital, and the Fourth Hospital of Hebei Medical University from 2010/02/01 to 2018/09/24, and all carried the germline BRCA1/2 pathogenic mutation. The patient did not receive any maintenance regimen, such as PARPi, bevacizumab, etc., after first- and second-line platinum therapy. The secondary PFI was more than 6 months in all patients. Patients enrolled in the study group were treated with PARPi monotherapy after secondary platinum-sensitive relapse and continued treatment until disease progression, demonstrating resistance to PARPi. Patients in control group were treated with platinum-based chemotherapy after secondary platinum-sensitive relapse, without restriction on the specific type and dose of

platinum. After progression of PARPi, patients treated with subsequent platinum-based chemotherapy were enrolled in study group 2; Among patients in control group, patients with PFI[?]6 months after third-line chemotherapy, and receiving subsequent platinum-based chemotherapy were enrolled in control group 2, and patients with PFI<6 months were enrolled in control group 3.

The determination of response of PARPi and platinum-based chemotherapy were in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria; If clinical data were insufficient for RECIST criteria assessment, the GCIG's CA125 criteria were used as an alternative[12].

PFS was defined as third-line therapy (including PARPi monotherapy and platinum-based chemotherapy) to disease progression or death, TFST was defined as the time from fourth-line chemotherapy to next subsequent therapy or death. PRS refers to the survival time after secondary platinum-sensitive relapse. Additional clinical data were collected including age at diagnosis, primary tumor location, CA-125 level at secondary relapse, neoadjuvant chemotherapy, pathological type, BRCA1/2 germline mutational status, platinum-based chemotherapy regimens, PARPi duration, efficacy and toxicity, primary and secondary PFI, and survival.

Germline BRCA1/2 detection

The protocol of germline BRCA1/2 detection based on NGS technology included the following six steps, namely, sample acquisition and processing, nucleic acid extraction, library construction, sequencing, data analysis and mutation interpretation, and each step included corresponding quality control steps. For amplicon based and hybridization capture methods, the detection regions included the entire exon coding region of BRCA1/2 gene and the exon-intron interface region (±20 base pairs). The average depth of each run was over 200×. Sanger DNA sequencing was performed for all reported variations using specific gene primers. All point mutations and small indels were confirmed by sanger DNA sequencing using specific gene primers, and the large fragment rearrangements were detected by multiplex ligation-dependent probe amplification (MLPA) methods. Variants were named according to HGVS nomenclature, and guidelines for the interpretation of sequence variants into 5-class system adapted from the International Agency for Research on Cancer[13, 14].

Statistical analyses

Student's t-test was used to compare differences in continuous variables with normal distribution. Differences in clinical characteristics and survival between defined groups of patients were assessed using chi-square test and Kaplan–Meier methods, where appropriate, and hazard ratios (HR) with 95% confidence intervals (CI) were calculated. In univariate analysis, p value 0.10 was defined as the upper limit for inclusion in multivariate analysis, in the latter, p<0.05 was considered significant. The SPSS program (version 16.0) was used for all statistical analysis. The significance levels were * $p < 0.05$ and ** $p < 0.01$, respectively.

Results

PARPi monotherapy was comparable to platinum-based chemotherapy in patients with secondary platinum-sensitive relapse.

A total of 64 patients were eligible for this retrospective analysis, including 31 (48.4%) in the study group and 33 (51.6%) in the control group. The median age at diagnosis of enrolled patients was 49 years, and the majority (75.0%) of patients had BRCA1 mutations. The baseline characteristics of patients were shown in Table 1 and Table S1, and were generally well balanced in age of diagnosis (p=0.599), neoadjuvant chemotherapy followed by interval debulking surgery (NAC-IDS), FIGO stage (p=0.645), residual lesions of primary surgery (p=0.985), CA125 level at secondary platinum-sensitive relapse (p=0.356) or primary debulking surgery (PDS) (p=0.875), PFI after 1st(p=0.243) and 2nd (p=0.363) platinum-based chemotherapy.

Tumor response of PARPi monotherapy and platinum-based chemotherapy was the primary observation of this study. 28 patients (90.3%) with PARPi monotherapy were on medication for more than 6 months, and 11 patients (35.5%) for more than 12 months. All 31 patients in study group were evaluable and showed excellent outcomes, with 24 patients (77.4%) meeting the criteria for disease remission. Tumor evaluation

was available in 25 patients (75.8%) who received platinum-based chemotherapy, and disease remission was achieved in 21 patients (84.0%), which was comparable to PARPi monotherapy (p=0.538), and there was no statistical difference in median PFS between the two groups (Figure 2A; median PFS, 8.6 vs. 11.1 months, HR=0.89, p=0.679).

Due to the limitations of retrospective studies, we only collected comparisons of hematological toxicity between the two treatments. The incidence of hematologic toxicity [?] 3 CTCAE was similar in both groups, with no statistical difference (35.5% vs. 28.6%, p=0.602). Myelodysplastic syndromes (MDS) and acute myelocytic leukemia (AML) did not occur in patients treated with PARPi monotherapy at follow-up.

2. PARPi monotherapy after secondary platinum-sensitive relapse significantly prolonged post-recurrent survival.

Ten patients in control group were treated with PARPi in posterior lines and were not included in the survival analysis. The median duration of post-recurrent follow-up for survival analysis was 30.0 months in PARPi monotherapy group, and 27.0 months in control group. Treatment with PARPi monotherapy resulted in a 65% reduction in the risk of death compared with control group (Figure 2B; HR=0.35, 95% Cl 0.14 to 0.87, p=0.024), and the median PRS was not reached (NR) in the PARPi monotherapy group compared with 33.3 months in the control group.

Univariate analysis was performed, and included the following variables: age at diagnosis, BRCA1/2 mutation status, PARPi monotherapy or not, residual lesions (R0, no residual lesions; R1, residual lesions less than 1 cm; R2, residual lesions more than 1 cm), FIGO stage, NAC-IDS or PDS, CA-125 level at secondary recurrence, primary and secondary PFI, and the results were shown in Table S2. Variables significantly associated with PRS included PARPi monotherapy vs. platinum-based chemotherapy (HR=0.36, 95%CI 0.15-0.92, p=0.032) and residual lesions (R0 vs. R1/R2, HR=0.29, 95%CI 0.11-0.78, p=0.014). In the multivariate analysis, FIGO stage at diagnosis was additionally included (I or II vs. III or IV, HR=0.18, 95%CI 0.24-1.35, p=0.096), and the results showed that PARPi monotherapy remained significant (HR=0.33, 95%CI 0.12-0.94, p=0.038), whereas residual lesions (R0 vs. R1/R2, HR=0.42, 95%CI 0.15-1.17, p=0.097) and FIGO stage at diagnosis (I or II vs. III or IV, HR=0.33, 95%CI 0.04-2.74, p=0.305) showed no statistical significance.

3. PARPi monotherapy had no negative effect on subsequent platinum-based chemotherapy and could improve prognosis.

27 patients with a median PFI of 20.2 months were treated with subsequent platinum-based chemotherapy after PARPi progression, and were enrolled in study group 2 ; Among the 23 patients in the control group without PARPi history, PFI of 22 patients after third-line platinum-based chemotherapy was obtained, including 14 platinum-sensitive relapsed patients (PFI[?]6 months), 13 of whom underwent subsequent platinum-based chemotherapy (Control group 2), and 8 platinum-resistant relapsed patients (PFI<6 months, Control group 3). The baseline characteristics of the patients were shown in Table 2 and Table S3. We compared the TFST of patients with platinum-based chemotherapy after the progression of PARPi and with patients in control group 2, and the result showed no statistical difference (Figure 2C; mTFST: 7.5 vs. 7.1 months, HR=1.11, p=0.800). Further survival analysis showed that PRS of patients in study group 2 was similar to platinum-sensitive relapse patients after third-line platinum chemotherapy (Figure 2D; mPRS: NR vs. 42.2 months, HR=0.66, p=0.503), and superior to platinum-resistant relapse patients after third-line platinum chemotherapy (Figure 2D; mPRS: NR vs. 23.7 months, HR=0.15, p=0.009).

Discussion

At present, a variety of PARP inhibitors have been used in the clinical treatment of ovarian cancer patients, covering several stages of treatment, which has become an epoch-making breakthrough in the history of ovarian cancer treatment. To our knowledge, this is the first study on the therapeutic effect of PARPi monotherapy compared with platinum-based chemotherapy, and the impact to subsequent platinum-containing chemotherapy and survival after the progression of PARPi in BRCA1/2 mutant patients with

secondary platinum-sensitive relapse.

PARPi monotherapy for relapsed ovarian cancer with BRCA1/2 mutations has been proven clinically and has been validated in several clinical studies. In BRCA1/2 mutant patients with platinum-sensitive relapse who received at least two lines of platinum-based chemotherapy, the ORR ranged from 56.0% with niraparib to 80.0% with rucaparib[15-19]. However, ovarian cancer patients with BRCA1/2 mutations were inherently more sensitive to platinum-based chemotherapy than patients with wild-type ovarian cancer[20], and the benefits of using PARPi inhibitors versus platinum-based chemotherapy at the same relapse stage were still uncertain. In our study, for patients with secondary platinum-sensitive relapse, the ORR was 77.4% and 84.0%, and the median PFS was 8.6 and 11.1 months, respectively. The therapeutic effect of PARPi monotherapy and platinum-based chemotherapy was equivalent.

The mechanisms of PARPi and platinum-based chemotherapy are both related to DNA damage repair, and the drug resistance mechanisms of PARPi include alterations in DNA damage repair, reactivation of HR, and replication fork protection, etc[8]. Theoretically, PARPi resistance may lead to subsequent platinum-based chemotherapy resistance. In Joo Ern's study[21], BRCA1/2 mutation patients who received 3-11 lines of platinum-based chemotherapy before Olaparib were included. After Olaparib resistance, the ORR of platinum-based chemotherapy was 40% (19/48), and the median PFS was 22 weeks, suggesting that there was still a partial response to platinum-based chemotherapy after PARPi resistance. Another study found that both platinum and non-platinum chemotherapy had a response rate after resistance of PARPi maintenance therapy, with median PFS of 7.0 and 8.5 months, respectively[22]. In our study, the PFI was significantly prolonged after PARPi monotherapy, and the median TFST of subsequent platinum-based chemotherapy after PARPi resistance was 7.5 months, consistent with patients in control group with platinum-sensitive relapse after third-line platinum-based chemotherapy. Further survival analysis confirmed that PRS of patients in the study group was similar to platinum-sensitive relapse patients, and superior to platinum-resistant relapse patients after third-line platinum chemotherapy. This result verified to some extent that although platinum-based chemotherapy had cross-resistance with PARPi, it does not negatively affect the efficacy of platinum-based chemotherapy after the progression of PARPi monotherapy.

PFS is currently the most widely used primary endpoint in clinical trials of PARP inhibitors. Most clinical studies have been conducted in recent years, so data on OS are still limited. In a phase 2 trial of Olaparib maintenance therapy, for patients with BRCA1/2 mutations, median PFS was significantly longer than placebo group (11.2 vs 4.3 months)[23], but the OS benefit (29.8 vs 27.8 months) was not statistically significant[24]. In the Olaparib SOLO-2 trial, maintenance treatment with Olaparib extended the median OS by 12.9 months compared with placebo in patients with relapsed platinum-sensitive BRCA1/2-mutant ovarian cancer[6]. In the NOVA study, in the same cohort as the SOLO2 trial, maintenance therapy with Niraparib provided a 15.5-month benefit for PFS[25], but no benefit for OS (43.6 vs 41.6 months)[26]. Results from the SOLO1 trial showed that Olaparib maintenance therapy extended the median PFS by 42 months compared to placebo in women with newly diagnosed advanced BRCA1/2 mutant ovarian cancer, although OS data are not yet available, it is expected that OS will benefit from a large increase in PFS as well[27]. For other PARPi, as well as for patients with other indications, the benefits of OS remain to be determined. In our study, patients with secondary platinum-sensitive relapse were selected and the results showed that the benefit of subsequent platinum-based chemotherapy was not negatively affected after the progression of PARPi monotherapy, and there was still a significant extension of PRS, which reduced the risk of death by 65%.

Factors affecting survival of ovarian cancer patients included tumor histology, FIGO stage, BRCA mutation status, ascites, and whether no residual lesions could be achieved after primary debulking surgery[28]. In a study with up to 10 years of follow-up, the initial survival advantage in patients with BRCA1/2 mutations may reflect a higher initial sensitivity to chemotherapy, but this response does not predict long-term survival, the strongest predictor of long-term survival was no residual lesions at resection[29]. In our study, we found that the factors affecting PRS included R0 resection and PARPi monotherapy, after incorporating FIGO stage for multivariate analysis, PARPi monotherapy was the independent prognostic factor, which also reflected

the superior therapeutic effect of PARPi monotherapy compared with R0 resection.

To a certain extent, our research has significant advantages. First, this is the first study to evaluate benefits of PARPi monotherapy versus platinum-based chemotherapy at the same relapse stage of BRCA1/2 mutant patients. In addition, the four-line treatment information was collected, at a stage with little evidence for treatment, besides, data of patients who did not receive PARPi treatment before as control group were difficult to obtain. However, the most significant limitation of our retrospective study was the limited number of patients. BRCA1/2 mutations account for less than 30% of ovarian cancer patients[30], and those who did not met the criteria for secondary platinum-sensitive relapse were excluded, as were those on maintenance therapy with PARPi or bevacizumab. Although the results of the analysis in our study were significantly different, further studies with large samples should be necessary. The findings of this study were applied only to a specific subset of the ovarian cancer patient population, not to all patients in general.

Conclusion

For patients with BRCA1/2-mutated ovarian cancer with secondary platinum-sensitive recurrence, the therapeutic effect of PARPi monotherapy and platinum-based chemotherapy was equivalent. PARPi monotherapy does not negatively affect the efficacy of subsequent platinum-based chemotherapy after the progression of PARPi monotherapy and could improve prognosis.

Declaration of interests

The authors have no conflicts of interests to disclose.

Contribution to authorship

Lingying Wu and Kun Song: Study design; Yana Ma, Ning Li and Hualei Bu: Wrote and edited the article; Chengjuan Jin: Assisted in editing the article; Yongwen Huang, Chengjuan Jin, Hao Wen, Shuai Feng, Hui Zhang, Beihua Kong: Provision of resources. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Details of ethics approval

This study was based on the statement of ethical principles in the Declaration of Helsinki. The Medical Ethics Committee of Qilu Hospital of Shandong University approved this study (KYLL-2017-133) on February 21, 2017. The study protocol was approved by the ethical review boards of the participating institutions, and signed consent was obtained from each patient.

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Data availability

All the original data of this study were available upon reasonable request to the corresponding author (*songkun2001226@sdu.edu.cn*), including, but not limited to, the request for repeating the results in this manuscript.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article

Table S1. Baseline characteristics of patients with secondary platinum-sensitive relapse

Table S2. The association of baseline factors with post-recurrence survival in patients treated with PARPi monotherapy and platinum-based chemotherapy.

Table S3. Baseline characteristics of patients with fourth-line treatment.

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Table1. Baseline characteristics of patients with secondary platinum-sensitive relapse

	Study Group (n = 31)	**Study Group (n = 31**
Age at diagnosed (years)		
49 years	18 (58.1%)	18 (58.1%)
>49 years	13 (41.9%)	13 (41.9%)
BRCA-germline-mutation status		
BRCA1 mutation	22 (71.0%)	22 (71.0%)
BRCA2 mutation	8 (25.8%)	8 (25.8%)
Both BRCA1 and 2 mutations	1 (3.2%)	1 (3.2%)
NAC-IDS		
Yes	7 (22.6%)	7 (22.6%)
No	24 (77.4%)	24 (77.4%)
FIGO stage at diagnosed		
I/II	5 (16.1%)	5 (16.1%)
III/IV	26 (83.9%)	26 (83.9%)
Primary tumor location		
Ovary	30 (96.8%)	30 (96.8%)
Fallopian tube	1 (3.2%)	1 (3.2%)
Histologic type		
High-grade serous	30 (96.8%)	30 (96.8%)
Serous not specified	0 (0.0%)	0 (0.0%)
Endometrioid	1 (3.2%)	1 (3.2%)
Clear-cell	0 (0.0%)	0 (0.0%)
Residual lesions		
No	16 (51.6%)	16 (51.6%)
Yes	10 (32.3%)	10 (32.3%)
Unknown [a]	5 (16.1%)	5 (16.1%)
PFI after 1st line of platinum-containing chemotherapy		
5-6months	2 (6.5%)	2 (6.5%)
6, <12 months	7 (22.6%)	7 (22.6%)
12 months	22(71.0%)	22(71.0%)
PFI after 2nd line of platinum-containing chemotherapy		
6, <12 months	23 (74.2%)	23 (74.2%)
12 months	8 (25.8%)	8 (25.8%)
CA125 level at secondary platinum-sensitive relapse		
70 U/ml	8 (25.8%)	8 (25.8%)
>70 U/ml	23 (74.2%)	23 (74.2%)
Unknown [a]	0 (0.0%)	0 (0.0%)
Tumor response		
PR/CR	24 (77.4%)	24 (77.4%)
SD/PD	7 (22.6%)	7 (22.6%)
Unknown [a]	0 (0.0%)	0 (0.0%)
Duration of PARPi treatment	Duration of PARPi treatment	
<6 months	<6 months	3 (9.7%)
6, <12 months	[?]6, <12 months	17 (54.8%)
12 months	[?]12 months	11 (35.5%)
Hematological toxicity ([?] 3 CTCAE)	Hematological toxicity ([?] 3 CTCAE)	

	Study Group (n = 31)	**Study Group (n = 31**
Yes	Yes	11 (35.5%)
No	No	20 (64.5%)
Unknown [a]	Unknown [a]	0 (0.0%)

[a] Data identified as unknown were not included in the difference analysis between the two groups.

Table2. Baseline characteristics of patients with fourth-line treatment.

	Study Group 2 (n = 27)	**Control Group 2 (n=13)**	**p-value**	**Control Group 3 (n=8)**	**p-value**
Age at diagnosed (years)					
[?]49 years	17 (63.0%)	4 (30.8%)	0.056	5 (62.5%)	0.981
>49 years	10 (37.0%)	9 (69.2%)		3 (37.5%)	
BRCA-germline-mutation status					
BRCA1 mutation	18 (66.7%)	10 (76.9%)	0.687	6 (75.0%)	0.817
BRCA2 mutation	8 (29.6%)	3 (23.1%)		2 (25.0%)	
BRCA1 and 2 mutations	1 (3.7%)	0 (0.0%)		0 (0.0%)	
NAC-IDS					
Yes	5 (18.5%)	5 (38.5%)	0.173	0 (0.0%)	0.189
No	22 (81.5%)	8 (61.5%)		8 (100.0%)	
FIGO stage at diagnosed					
I/II	4 (14.8%)	2 (15.4%)	0.962	2 (25.0%)	0.502
III/IV	23 (85.2%)	11 (84.6%)		6 (75.0%)	
Primary tumor location					
Ovary	26 (96.3%)	13 (100.0%)	0.482	7 (87.5%)	0.347
Fallopian tube	1 (3.7%)	0 (0.0%)		1 (12.5%)	
Histologic type					
High-grade serous	26 (96.3%)	12 (92.3%)	–	6 (75.0%)	–
Serous not specified	0 (0.0%)	0 (0.0%)		2 (25.0%)	
Endometrioid	1 (3.7%)	0 (0.0%)		0 (0.0%)	
Clear-cell	0 (0.0%)	1 (7.7%)		0 (0.0%)	
Residual lesions					
No	15 (55.6%)	8 (61.5%)	0.932	5 (62.5%)	0.890
Yes	8 (29.6%)	4 (30.8%)		3 (37.5%)	
Unknown [a]	4 (14.8%)	1 (7.7%)		0 (0.0%)	

	Study Group 2 (n = 27)	**Control Group 2 (n=13)**	**p-value**	**Control Group 3 (n=8)**	**p-value**
PFI after 1st line of platinum-containing chemotherapy					
5-6months	2 (7.4%)	0 (0.0%)	0.222	0 (0.0%)	0.547
[?]6, <12 months	6 (22.2%)	6 (46.2%)		3 (37.5%)	
[?]12 months	19 (70.4%)	7 (53.8%)		5 (62.5%)	
PFI after 2nd line of platinum-containing chemotherapy					
[?]6, <12 months	20 (74.1%)	8 (61.5%)	0.418	5 (62.5%)	0.525
[?]12 months	7 (25.9%)	5 (38.5%)		3 (37.5%)	
PFI before fourth-line chemotherapy					
<6 months	0(0.0%)	0(0.0%)	–	8(100.0%)	0.000**
[?]6, <12 months	1(3.7%)	11(84.6%)		0(0.0%)	
[?]12 months	26 (96.3%)	2(15.4%)		0(0.0%)	

[a] Data identified as unknown were not included in the difference analysis between the two groups.

** p <0.01

Table S1. Baseline characteristics of patients with secondary platinum-sensitive relapse

	Study Group (n = 31)	**Study Group (n = 31)**	**Control Group (n**
Chemotherapy regimens of 3rd line	Chemotherapy regimens of 3rd line		
Carboplatin based	Carboplatin based	–	–
Nedaplatin based	Nedaplatin based	–	–
Cisplatin based	Cisplatin based	–	–
Oxaliplatin based	Oxaliplatin based	–	–
Lobaplatin based	Lobaplatin based	–	–
Multiple platinum	Multiple platinum	–	–

[a] Carboplatin+oxaliplatin: 2 patients;

Cisplatin+nedaplatin/lobaplatin/carboplatin: 3 patients; Nedaplatin+lobaplatin: 1 patient.

Table S2. The association of baseline factors with post-recurrence survival in patients treated with PARPi monotherapy and platinum-based chemotherapy.

	Univariate	**Univariate**	**Multivariate**	**Multivariate**	**Multivariate**
	HR(95% Cl)	**p-value**	**p-value**	**HR(95%Cl) p-value**	**HR(95%Cl) p-value**
Age([?]49 vs. >49 years)	0.71 (0.29-1.72)	0.451	0.451	–	–
PARPi monother-apy (Yes vs. No)	0.36 (0.15-0.92)	0.032*	0.032*	0.33 (0.12-0.94)	0.038*
Residual Le-sions(R0 vs. R1+R2)	0.29 (0.11-0.78)	0.014*	0.014*	0.42 (0.15-1.17)	0.097
BRCA mutation (1 vs. 2)	0.60 (0.17-2.07)	0.416	0.416	–	–
Stage at diagnosis (I or II vs. III or IV)	0.18 (0.24-1.35)	0.096	0.096	0.33 (0.04-2.74)-	0.305
Cytoreductive surgery (NAC-IDS vs. PDS)	0.42 (0.12-1.47)	0.174	0.174	–	–
1st PFI (5-12 vs. >12 months)	0.56 (0.23-1.38)	0.208	0.208	–	–
2nd PFI (6-12 vs. >12 months)	0.58 (0.19-1.75)	0.334	0.334	–	–
CA-125 at secondary recurrence ([?]70 vs. >70 U/ml)	0.62 (0.21-1.88)	0.400	0.400	–	–

* p <0.05

Table S3. Baseline characteristics of patients with fourth-line treatment.

	Study Group 2 (n = 27)	**Control Group 2 (n=13)**	**p-value**
Chemotherapy regimens of fourth-line treatment			
Carboplatin based	14 (51.9%)	4 (30.8%)	–
Nedaplatin based	6 (22.2%)	4 (30.8%)	

	Study Group 2 (n = 27)	Control Group 2 (n=13)	p-value
Cisplatin based	2 (7.4%)	0 (0.0%)	
Oxaliplatin based	1 (3.7%)	0 (0.0%)	
Lobaplatin based	1 (3.7%)	3 (23.1%)	
Multiple platinum	3[a] (11.1%)	2[b] (15.4%)	

[a] Carboplatin+Oxaliplatin: 1 patient; Nedaplatin+Lobaplatin: 2 patients.

[b] Carboplatin+Cisplatin/Lobaplatin:2 patients.