THERAPEUTIC ADVANCES in
Medical Oncology

Original Research

Oxaliplatin prior to PARP inhibitor in BRCA-mutated ovarian cancer

Ther Adv Med Oncol

2023, Vol. 15: 1–10

DOI: 10.1177/17588359231173181

Maria Ornella Nicoletto, Alessandra Baldoni, Francesco Cavallin, Andrea Grego, Cristina Falci, Margherita Nardin, Enzo Mammano, Eleonora Lai and Valter Torri

Abstract

Background: The use of PARP inhibitor (PARPi) has shown a considerable benefit in progression-free survival (PFS) in relapsed, platinum-sensitive epithelial ovarian cancer (OC).

Objective: Our study aimed to investigate the impact of the last platinum-based chemotherapy treatment in response to PARPi.

Design: Retrospective cohort study.

Patients and methods: The study involved 96 consecutive, pretreated, platinum-sensitive advanced OC patients. Demographics and clinical data were retrieved from clinical records. PFS and overall survival (OS) were calculated from the start of PARPi.

Results: Germline BRCA mutation was investigated in all cases. Platinum-based chemotherapy before PARPi maintenance therapy included pegylated liposomal doxorubicin-oxaliplatin (PLD-Ox) in 46 patients (48%) and other platinum-based chemotherapy in 50 patients (52%). During a median follow-up of 22 months from the beginning of PARPi therapy, 57 patients relapsed (median PFS: 12 months) and 64 patients died (median OS: 23 months). During multivariable analysis, receiving PLD-Ox before PARPi was associated with improved PFS [hazard ratio (HR): 0.46, 95% CI: 0.26–0.82] and OS (HR: 0.48, 95% CI: 0.27–0.83). In 36 BRCA-mutated patients, PLD-Ox was associated with improved PFS (2-year PFS: 70.0% *versus* 25.0%, $p = 0.02$).

Conclusion: Receiving PLD-Ox before PARPi may improve prognosis in platinum-sensitive advanced OC patients and may provide advantages in the BRCA-mutated subgroup.

Keywords: BRCA mutated, PARP inhibitors, oxaliplatin, pegylated liposomal doxorubicin, platinum-sensitive epithelial ovarian cancer

Received: 22 April 2022; revised manuscript accepted: 13 April 2023.

Correspondence to:
Maria Ornella Nicoletto
Medical Oncology 2, Istituto Oncologico Veneto IRCCS, via Gattamelata 64, Padova, 35121, Italy
nicolettomariaornella@gmail.com

Alessandra Baldoni
Department of Medical Oncology, AULSS 3 Serenissima, Mirano Hospital, Mirano, (VE), Italy

Francesco Cavallin
Independent statistician, Solagna (VI), Italy

Andrea Grego
Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy

Cristina Falci
Eleonora Lai
Medical Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Italy

Margherita Nardin
Radiology department, Istituto Oncologico Veneto IRCCS, Padova, Italy

Enzo Mammano
Department of Surgery, Ospedale Sant'Antonio, Padova, Italy

Valter Torri
Laboratory of Methodology for Clinical Research, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italy

Introduction

According to the European Institute of Women's Health, ovarian cancer (OC) results in more than 42,700 deaths annually in Europe.[1] In Italy, there were approximately 3260 deaths recorded in 2016 and 5300 new cases of OC in 2019.[2,3] Approximately 80% of patients with new diagnosis of OC have a response to taxane-platinum chemotherapy. However, recurrent disease develops in high percentage of patients[4] and brings need for new knowledge and innovative therapeutic approaches.

The introduction of novel class drugs, namely PARP inhibitor (PARPi), plays an important role in BRCA-mutated OC, as PARPi eliminates an alternative DNA repair pathway leading to tumor cell death. Olaparib is the first oral PARPi that induces synthetic lethality in BRCA one-half deficient tumor cells.[5,6] Niraparib is a highly selective inhibitor of polyadenosine diphosphate (ADP-ribose) polymerase (PARP) 1 and 2. These nuclear proteins detect DNA damage.[7]

Olaparib and niraparib are the most used PARP inhibitors.[8–10] While olaparib demonstrated an improved progression-free survival (PFS) exceeding 49.8 months in maintenance therapy, first line in BRCA-mutated OC patients in SOLO1 trial,[8] bevacizumab-olaparib showed a PFS of 37.2 months in the Platine, Avastin and OLAparib in 1st Line (PAOLA-1) trial[9] and niraparib showed a PFS of 22.1 months in the Partnership for Research and Innovation in the Mediterranean Area (PRIMA) study[11] (Table 1).

Table 1. Median PFS in maintenance therapy in first-line OC: review of the literature.

Study	Year	BRCA genotype	Therapeutic arm PFS (months)	Maintenance	Comparator arm PFS (months)	Type of comparator	*p*-Value
Markmann *et al.*[12]	2009	All patients	22	12 Paclitaxel cycles	14	3 Paclitaxel cycles	0.006
Burger *et al.*[13]	2011	All patients	14.1	Bevacizumab	10.3	Placebo	<0.001
AGO-OVAR16[14]	2019	All patients	17.9	Pazopanib	12.3	Placebo	0.002
PAOLA1[9]	2019	All patients	26.1	Bevacizumab + Olaparib	18.3	Bevacizumab	<0.001
PRIMA[11]	2019	All patients	21.9	Niraparib	10.4	Placebo	<0.001
BRCA wild-type OC patients							
PAOLA1[9]	2019	BRCA–	18.9	Bevacizumab + Olaparib	16.0	Bevacizumab	<0.001
PRIMA[11]	2019	BRCA–	19.6	Niraparib	8.2	Placebo	<0.001
Only BRCA mutation OC patients							
SOLO 1[8]	2018	BRCA +	>49.8	Olaparib	13.8	Placebo	<0.001
PAOLA1[9]	2019	BRCA +	37.2	Bevacizumab + Olaparib	21.7	Bevacizumab	<0.001
PRIMA[11]	2019	BRCA+	22.1	Niraparib	10.9	Placebo	<0.001

All patients, platinum-sensitive patients (with or without BRCA mutation); BRCA+, patients with BRCA mutation; BRCA–, patients without BRCA mutation; OC, ovarian cancer; PFS, progression-free survival.

Table 2. Median PFS in maintenance therapy with PARPi in platinum-sensitive ovarian cancer as second line: review of the literature.

	Year	Patients	Therapeutic arm PFS (months)	Maintenance	Placebo arm PFS (months)	*p*-Value
OCEANS[15]	2012	All patients	12.4	Bevacizumab	8.4	<0.001
ICON6[16]	2016	All patients	11	Cediranib	8.7	<0.001
NOVA[10]	2016	BRCA–	9.3	Niraparib	3.9	<0.001
BRCA-mutated only patients						
Ledermann *et al.*[17]	2014	BRCA+	11.2	Olaparib	4.3	<0.001
NOVA[10]	2016	BRCA+	21	Niraparib	5.5	<0.001
SOLO2[18]	2017	BRCA+	19.1	Olaparib	5.5	<0.001
ARIEL 3[19]	2017	BRCA+	16.6	Rucaparib	5.4	<0.001
SOLO3[20]	2020	BRCA+	13.4	Olaparib	CT* = 9.2	0.013

All patients, platinum-sensitive patients (with or without BRCA mutation); BRCA+, patients with BRCA mutation; BRCA–, patients without BRCA mutation; CT*, non-platinum chemotherapy; PFS, progression-free survival.

Table 2 offers a literature overview of PFS after PARPi maintenance therapy in platinum-sensitive OC as second line. Other non-comparative studies with olaparib and niraparib maintenance in poly-treated population showed PFS between 5.5 and 7 months.[21–23]

Oxaliplatin is a common antiblastic different from carboplatin and cisplatin, with a mechanism of action that allows efficacy in platinum-resistant patients, and without dose-limiting toxicity such as neurological and renal which may occur in patients treated with carboplatin or cisplatin.[24,25] The National Comprehensive Cancer Network Guidelines includes the use of oxaliplatin as an active drug in the therapy of recurrent OC.[26] Given the heterogeneous results in literature, it is reasonable to wonder whether treatment options before PARPi may contribute to such heterogeneity. This study aimed to investigate the impact of the last platinum-based chemotherapy treatment in response to PARPi. We hypothesized that oxaliplatin may provide some advantages in BRCA-mutated OC as shown in other genetic neoplasms such as colon cancer in Lynch's syndrome,[27] and in a previous study reporting improved survival in patients with a germline BRCA1 or BRCA2 mutation and/or positive cancer family history.[28]

Materials and methods

Study design

This is a retrospective, single-institutional, cohort study on the impact of the last platinum-based chemotherapy treatment (PLD-Ox *versus* other platinum-based chemotherapy) in response to PARPi in platinum-sensitive advanced OC patients. The comparison between the chemotherapy regimens was planned a priori and was not the result of selective reporting. The study included all consecutive patients treated with PARPi maintenance between April 2014 and March 2020 at the IOV-IRCCS in Padua (Italy).

Patients

Eligible patients had histologically diagnosed ovarian, fallopian tube cancer predominantly high-grade serous pathology. The stage was III or IV, with or without BRCA mutation determined with genetic analysis (Myriad Genetics). All patients were platinum-sensitive and had received at least two such regimens with platinum with/without bevacizumab and/or trabectedin. Platinum-based chemotherapy consisted of carboplatin or cisplatin-gemcitabine, or platinum (cisplatin/carboplatin)-paclitaxel, or pegylated liposomal doxorubicin-oxaliplatin (PLD-Ox) or cisplatin/carboplatin alone according to professional treatment dosage.

Treatment

PARPi treatment started within 8 weeks after last platinum cycle: olaparib for BRCA-positive OC patients,[8] 800 mg capsules and then 600 mg tablets, was reduced to 500 mg in case of severe anemia or persistent nausea G3 (ECOG). Niraparib dose was 300 mg daily for patients, without BRCA mutation, >77 kg and/or with platelet count $>150{,}000/mm^3$, and it was reduced to 200 mg for patients <77 kg and/or with platelet count $\leqslant 150{,}000$.[10] Dose reduction was mandatory in cases of developing thrombocytopenia or anemia grade 3 or 4 ECOG, and additional reduction up to 100 mg niraparib/400 mg olaparib was permitted in case of anemia or nausea grade 3 or 4 ECOG.

Safety for niraparib was monitored weekly in the first month and then monthly, while for olaparib monthly.

Niraparib or olaparib were continued until disease progression or unacceptable grade 4 toxicity according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Treatment could be interrupted for up to 28 days for hematological adverse events; after the resolution of toxicity treatment could be restarted at reduced dose according to criteria to manage adverse events and minimize drug discontinuation.[8,10,11,18]

Assessment

Baseline imaging with the use of abdominopelvic CT scan, MRI, or abdominal echography was to be performed within 30 days from the start of chemotherapy for relapse. Disease measures were evaluated after four cycles of platinum chemotherapy; if responsive, the patient would start PARPi; if stable, she would continue with another 3–4 cycles and start PARPi after a minimal response. Physical examination was performed at the beginning of each chemotherapy cycle, then during PARPi every month in the first 6 months of maintenance, then every 3 months. Disease progression was determined according to Response Evaluation Criteria in Solid Tumors.[29] Toxicity was graded according to CTCAE 5.0.

Data collection

Data collection included age; BRCA mutation status; pre-PARPi Ca 125 serum level; neoplastic residuum; pretreatment with bevacizumab and/or with trabectedin; last chemotherapy with

platinum prior to PARPi and number of cycles; date of start of PARPi; disease progression and date of occurrence; patient status (alive/deceased) and date of last follow-up or death. All data were retrieved from clinical records.

Statistical analysis

Continuous variables were summarized as median and interquartile range (IQR), and categorical variables as frequency and percentage. Baseline characteristics were compared between patients receiving PLD-Ox and those receiving other platinum-based chemotherapy using Mann-Whitney test (continuous variables) and Chi-square test or Fisher's exact test (categorical variables). PFS and overall survival (OS) were evaluated from the beginning of PARPi therapy to any radiologically confirmed progression, or to last follow-up or death from any cause, respectively. Survival curves were calculated with the Kaplan–Meier method and compared between groups using the log-rank test. Multivariable analyses of survival were performed using Cox regression models that included receiving PLD-Ox *versus* other platinum-based chemotherapy before PARPi and clinically relevant factors. Effect sizes were reported as hazard ratio (HR) with 95% confidence interval. Adjusted survival curves were calculated using the marginal approach with inverse probability weighting.[30] The logistic regressions used to derive the weights included BRCA mutation, residual disease, Ca125, pretreatment with trabectedin and/or bevacizumab, and pretreatment lines as covariates. All tests were two-sided and a p-value < 0.05 was considered significant. No adjustment for multiple testing was applied given the exploratory purpose of the study. Statistical analysis was performed using R 4.1 (R Foundation for Statistical Computing, Vienna, Austria).[31]

Results

The analysis included all consecutive 96 platinum-sensitive OC patients treated with 4–6 cycles of platinum in second, third, or further line, after CT scan or MRI, who began PARPi maintenance therapy during the study period. Patient characteristics are shown in Table 3. Complete response was achieved in two non-BRCA-mutated patients treated with PLD-Ox and one BRCA-mutated patient treated with other platinum-based chemotherapy (Gem-Jm8), while the others showed partial response or minimal change before starting PARPi.

Platinum-based chemotherapy before PARPi maintenance therapy included PLD-Ox in 46 patients (48%) and other platinum-based chemotherapy in 50 patients (52%). The treatments in the non-PLD-Ox cohort are reported in Supplemental Table S1. Baseline characteristics were comparable between these two groups, apart from the number of platinum-based cycles before PARPi (Table 3). In the 36 patients with BRCA-mutated OC, baseline characteristics were comparable between patients receiving PLD-Ox ($n = 20$) and those receiving other platinum-based chemotherapy ($n = 16$), apart from the number of platinum-based cycles before PARPi and a small imbalance regarding the prior lines of therapy (Supplemental Table S2). In the 60 patients with non-BRCA-mutated OC, baseline characteristics were comparable between patients receiving PLD-Ox ($n = 26$) and those receiving other platinum-based chemotherapy ($n = 34$) (Supplemental Table S3).

Median duration of follow-up from the beginning of PARPi therapy was 22 months (IQR 14–34) in all patients, 27 months (IQR 18–50) in BRCA-mutated OC patients, and 20 months (IQR 12–28) in non-BRCA-mutated OC patients.

During the follow-up, 57 patients relapsed (20 BRCA-mutated and 37 non-BRCA-mutated) and median PFS was 12 months (22 months in BRCA-mutated and 8 months in non-BRCA-mutated OC). Overall, 2-year PFS was 52.2% in patients receiving PLD-Ox and 33.0% in those receiving other platinum-based chemotherapy [$p = 0.06$; Figure 1(a)]. Of note, PLD-Ox was associated with improved PFS in BRCA-mutated OC patients (2-year PFS: 70.0% *versus* 25.0%, $p = 0.02$) but not in non-BRCA-mutated patients (2-year PFS: 38.5% *versus* 37.2%, $p = 0.70$) (Supplemental Figure S1). During multivariable analysis, PLD-Ox before PARPi (HR: 0.46, 95% CI: 0.26–0.82; $p = 0.008$), receiving $\leqslant 3$ pretreatment lines (HR: 0.50, 95% CI: 0.28–80; $p = 0.02$) and Ca125 $\leqslant 35$ U/mL (HR: 0.31, 95% CI: 0.16–0.59; $p = 0.0003$) were associated with improved PFS (Table 4). Adjusted survival curves for patients who received PLD-Ox and those who received other platinum-based chemotherapy are shown in Figure 2(a).

During the follow-up, 64 patients died (20 BRCA-mutated and 44 non-BRCA-mutated) and median OS was 23 months (40 months in BRCA-mutated and 20 months in non-BRCA-mutated). Overall,

Table 3. Baseline characteristics of all consecutive OC patients who received platinum-based chemotherapy before PARPi maintenance therapy.

Variable	All patients ($n=96$)	Patients treated with PLD-Ox[a] ($n=46$)	Patients treated with other platinum-based chemotherapy[b] ($n=50$)	p-Value
Age at start of PARPi, years[c]	64 (57–69)	64 (58–70)	64 (55–67)	0.43
Previous treatment with bevacizumab (%)	30 (31)	11 (24)	19 (38)	0.21
Previous treatment with trabectedin (%)	28 (29)	13 (28)	15 (30)	0.99
Residual disease >1 cm (%)	62 (65)	28 (61)	34 (68)	0.61
CA125 before PARPi (%)				
⩽35 U/ml	42/95 (44)	18 (39)	24/49 (49)	0.45
>35 U/ml	53/95 (56)	28 (61)	25/49 (51)	
Germline BRCA mutation (%)				
Negative	52 (54)	21 (45)	31 (62)	0.42
BRCA1	19 (20)	10 (22)	9 (18)	
BRCA2	17 (18)	10 (22)	7 (14)	
Variants	8 (8)	5 (11)	3 (6)	
N of platinum-based lines before PARPi (%)				
2–3 lines	63 (66)	29 (63)	34 (68)	0.77
>3 lines	33 (34)	17 (37)	16 (32)	
N of platinum-based cycles before PARPi (%)				
4 cycles	27 (28)	18 (39)	9 (18)	0.04
>4 cycles	69 (72)	28 (61)	41 (82)	
PARPi (%)				
Niraparib	60 (63)	26 (57)	34 (68)	0.34
Olaparib	36 (37)	20 (43)	16 (32)	

[a]Pegylated liposomal doxorubicin-oxaliplatin. [b]Carboplatin or cisplatin-gemcitabine, or platinum (cisplatin/carboplatin)-paclitaxel, or cisplatin/carboplatin alone. Data summarized as *n* (%) or [c]median (IQR).
OC, ovarian cancer; PARPi, PARP inhibitor.

2-year OS was 56.1% in patients receiving PLD-Ox and 38.7% in those receiving other platinum-based chemotherapy [$p=0.06$; Figure 1(b)]. Of note, PLD-Ox was closely associated with improved OS in BRCA-mutated OC (2-year OS: 79.2% *versus* 43.8%, $p=0.06$) but not in non-BRCA-mutated (2-year OS: 38.5% *versus* 36.8%, $p=0.60$) (Supplemental Figure S2). During multivariable analysis, PLD-Ox before PARPi (HR: 0.48, 95% CI: 0.27–0.83; $p=0.009$) and Ca125 ⩽ 35 U/mL (HR: 0.29, 95% CI: 0.16–0.54; $p<0.0001$) were associated with improved OS (Table 4). Adjusted survival curves for patients who received PLD-Ox and those who received other platinum-based chemotherapy are shown in Figure 2(b).

The number of platinum-based cycles before PARPi was not included in the survival models due to collinearity with PLD-OX ($p=0.03$) and BRCA mutation ($p=0.01$).

There were no on-treatment deaths in either group. Thirteen patients receiving olaparib (36%)

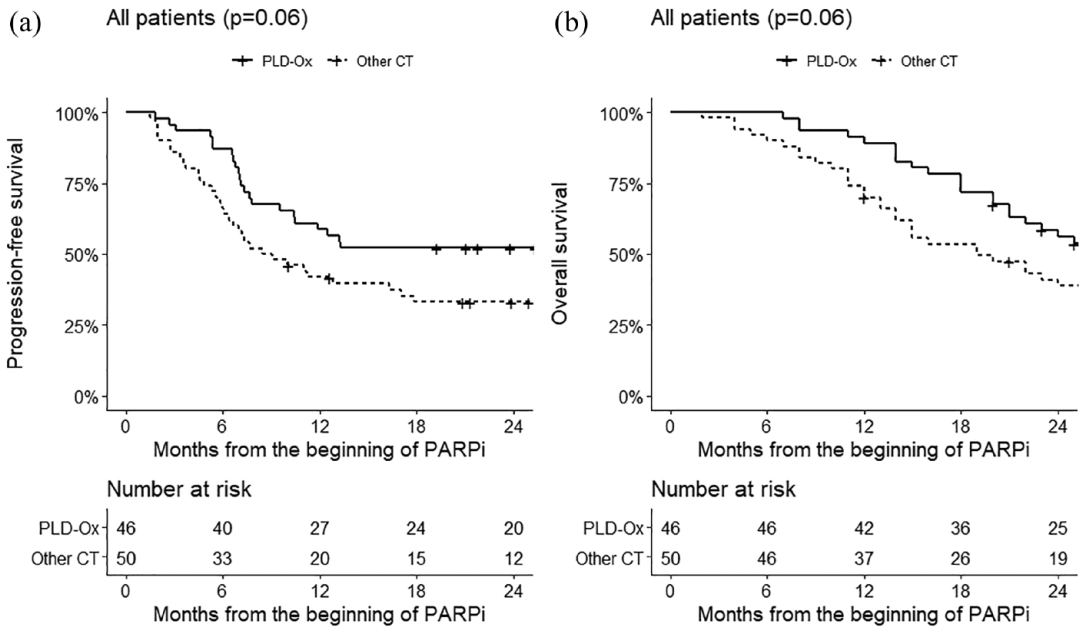

Figure 1. Progression-free survival (a) and overall survival (b) in OC patients who received PLD-Ox and in those who received other platinum-based chemotherapy.
OC, ovarian cancer; PLD-Ox, pegylated liposomal doxorubicin-oxaliplatin.

Table 4. Multivariable analysis of progression-free survival and overall survival in consecutive OC patients who received platinum-based chemotherapy before PARPi maintenance therapy.

Variables	Progression-free survival			Overall survival		
	Hazard ratio	95% confidence interval	*p*-Value	Hazard ratio	95% confidence interval	*p*-Value
PLD-Ox[a]	0.46	0.26–0.82	0.008	0.48	0.27–0.83	0.009
BRCA mutated	0.86	0.49–1.52	0.61	0.58	0.32–1.04	0.07
Residuum >1 cm	0.88	0.47–1.64	0.69	1.00	0.54–1.84	0.99
Ca125 ⩽ 35 U/mL	0.31	0.16–0.59	0.0003	0.29	0.16–0.54	<0.0001
Pretreatment with trabectedin and/or bevacizumab	1.49	0.83–2.65	0.18	1.49	0.86–2.57	0.15
⩽3 Pretreatment lines	0.50	0.28–0.89	0.02	0.68	0.39–1.17	0.16

The proportional hazards assumption was satisfied in both models. [a]Carboplatin or cisplatin-gemcitabine, or platinum (cisplatin/carboplatin)-paclitaxel, or cisplatin/carboplatin alone. PARPi, PARP inhibitors.

and 13 patients receiving niraparib (22%) had dose reduction. Side effects stratified by BRCA mutation and pre-PARPi treatment are summarized in Supplemental Table S4. During the follow-up, three patients in niraparib developed myelodysplastic syndrome: after 6 months of PARPi therapy, two of them presented early signs of myelodysplasia at the first subsequent gemcitabine-carboplatin and cisplatin monotherapy. They died from progression disease associated with myelodysplasia after 6 and 12 months, respectively. The third patient, after 12 months with 300 mg niraparib, presented persistent thrombocytopenia (70,000 platelets/mm^3) for 3 months, when

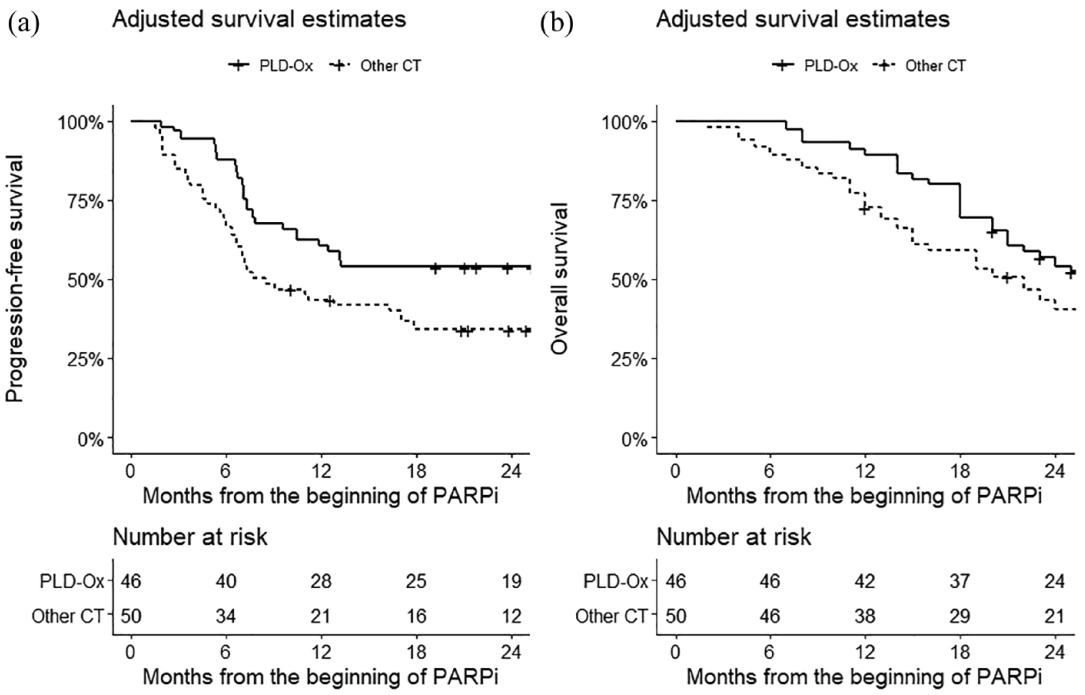

Figure 2. Adjusted survival curves for progression-free survival (a) and overall survival (b) in OC patients who received PLD-Ox and in those who received other platinum-based chemotherapy.
OC, ovarian cancer; PLD-Ox, pegylated liposomal doxorubicin-oxaliplatin.

fever and anemia appeared and bone marrow biopsy showed an acute myeloid leukemia, therefore the patient started hypomethylating therapy.

Among patients who received other platinum-based chemotherapy before PARPi, 2-year PFS was 27.3% in those who received PLD across any prior line and 34.4% in those who did not ($p = 0.20$); 2-year OS was 27.3% in those who received PLD across any prior line and 44.6% in those who did not ($p = 0.06$).

Discussion

To our knowledge, available literature offers no information on the relationship between pre-PARPi exposure to platinum agents and survival in OC patients. Our findings suggest that receiving PLD-Ox before PARPi may improve prognosis in platinum-sensitive advanced OC patients.

In our previous phase II study, we had described the efficacy of PLD-Ox for platinum-sensitive, BRCA-mutated OC patients or high risk for family history.[28,32] This 'old' treatment followed by the novel PARPi therapies showed a significant benefit in survival of BRCA-mutated epithelial OC patients, with a median PFS of 27 months and a median OS of 54 months, data in line with the survival of the patients who were part of the SOLO2/ENGOT-ov21 trial.[33]

Different from carboplatin or cisplatin, oxaliplatin in OC is known to be advantageous and to lack cross-resistance with cisplatin and carboplatin.[34] In a previous study, we showed that PLD-Ox combination can be active and feasible in this group of bone marrow often-frail women.[35] Other research confirmed the advantage of PLD in BRCA-mutated OC,[36–38] and the PLD-Ox combination has shown a favorable toxicity profile for low incidence of anemia.[28,32] PARPi after PLD-Ox caused anemia in only 15% BRCA-mutated OC patients, whereas occurrence of anemia was 43% in SOLO2 and 51% in SOLO3.[18,20]

We also confirmed previous reporting of improved survival in patients with lower level of Ca-125.[39]

This study has some limitations. First, the retrospective design precludes any causal association; hence, further prospective trials using a third type of platinum are warranted to confirm our results. Second, the single-center data collection

limits the generalizability of the findings to similar settings. Third, the limited sample size suggests caution in the interpretation of the results. For example, the small number of BRCA-mutated patients prevented any meaningful discussion on the clinical relevance of the observed differences between treatment subgroups. Nonetheless, the reader should note that BRCA-mutated patients in the PLD-Ox group received fewer prior lines and cycles of therapy before PARPi, which might be related to better outcome with PLD-Ox because it is more chemosensitive. A comparison between PLD-Ox and carboplatin-PLD might have been interesting, but unfortunately, the latter was administered only to few patients. Further studies with larger size may strengthen our findings and may also investigate a possible effect of the interaction between PLD-Ox followed by PARPi and BRCA mutation status on prognosis.

Conclusion

The results of our study highlight the benefit of PLD combined with oxaliplatin, the latter characterized by a broad spectrum of anticancer activity and a better safety profile than cisplatin, being an important alternative for platinum hypersensitivity, especially after multiple infusions.[40] Future prospective studies/clinical trials could be useful to investigate oxaliplatin in BRCA-mutated OC patients *versus* other combinations to show the advantage of oxaliplatin pre-PARPi.

Declarations

Ethics approval and consent to participate

The approval by an ethics committee was not required due to the observational, retrospective nature of the study and the use of anonymized data. The study complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the Good Clinical Practice guidelines, and the Declaration of Helsinki. The patients gave their consent to use their anonymized data for scientific purpose.

Consent for publication

Not applicable.

Author contribution(s)

Maria Ornella Nicoletto: Conceptualization; Writing – original draft; Writing – review & editing.

Alessandra Baldoni: Conceptualization; Data curation; Writing – original draft; Writing – review & editing.

Francesco Cavallin: Formal analysis; Writing – review & editing.

Andrea Grego: Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing.

Cristina Falci: Data curation; Methodology; Visualization; Writing – review & editing.

Margherita Nardin: Data curation; Methodology; Writing – original draft.

Enzo Mammano: Methodology; Visualization; Writing – review & editing.

Eleonora Lai: Methodology; Visualization; Writing – review & editing.

Valter Torri: Formal analysis; Writing – original draft.

Acknowledgment

The authors thank Giulia Tasca for the collaboration in the provision of the drug, and Szabo Beata for her help in revising the manuscript for grammar and syntax.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplemental material

Supplemental material for this article is available online.

References

1. European Institute of Women's Health. Policy brief: Women and ovarian cancer in the EU, https://eurohealth.ie/policy-brief-women-and-ovarian-cancer-in-the-eu-2018 (2018, accessed 1 March 2021).

2. Codifica delle cause di morte con L'ICD-10, versione 2016. https://www.istat.it/it/files//2011/01/codifica-delle-cause-di-morte-ICD10-2016.pdf. (2016, accessed 1 March 2021).
3. I numeri del cancro in Italia, https://www.aiom.it/wp-content/uploads/2019/09/2019_Numeri_Cancro-operatori-web.pdf (2019, accessed 1 March 2021).
4. Lheureux S, Gourley C, Vergote I, *et al.* Epithelial ovarian cancer. *Lancet* 2019; 393: 1240–1253.
5. Evers B, Drost R, Schut E, *et al.* Selective inhibition of BRCA2-deficient mammary tumor cell growth by AZD2281 and cisplatin. *Clin Cancer Res* 2008; 14: 3916–3925.
6. Fong PC, Boss DS, Yap TA, *et al.* Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* Mutation carriers. *New Engl J Med* 2018; 361: 123–134.
7. Jones P, Altamura S, Boueres J, *et al.* Discovery of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (MK-4827): a novel oral poly(ADP-ribose)polymerase (PARP) inhibitor efficacious in BRCA-1 and -2 mutant tumors. *J Med Chem* 2009; 52: 7170–7185.
8. Moore K, Colombo N, Scambia G, *et al.* Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *New Engl J Med* 2018; 379: 2495–2505.
9. Ray-Coquard I, Pautier P, Pignata S, *et al.* Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *New Engl J Med* 2019; 381: 2416–2428.
10. Mirza MR, Monk BJ, Herrstedt J, *et al.* Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *New Engl J Med* 2016; 375: 2154–2164.
11. González-Martín A, Pothuri B, Vergote I, *et al.* Niraparib in patients with newly diagnosed advanced ovarian cancer. *New Engl J Med* 2019; 381: 2391–2402.
12. Markman M, Liu PY, Moon J, *et al.* Impact on survival of 12 versus 3 monthly cycles of paclitaxel (175 mg/m^2) administered to patients with advanced ovarian cancer who attained a complete response to primary platinum-paclitaxel: follow-up of a Southwest Oncology Group and Gynecologic Oncology Group phase 3 trial. *Eur J Gynaecol Oncol* 2009; 114: 195–198.
13. Burger RA, Brady MF, Bookman MA, *et al.* Incorporation of bevacizumab in the primary treatment of ovarian cancer. *New Engl J Med* 2011; 365: 2473–2483.
14. Vergote I, du Bois A, Floquet A, *et al.* Overall survival results of AGO-OVAR16: a phase 3 study of maintenance pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced ovarian cancer. *Eur J Gynaecol Oncol* 2019; 155: 186–191.
15. Aghajanian C, Blank SV, Goff BA, *et al.* OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol* 2012; 30: 2039–2045.
16. Ledermann JA, Embleton AC and Raja F. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; 387: 1066–1074.
17. Ledermann J, Harter P, Gourley C, *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: 852–861.
18. Pujade-Lauraine E, Ledermann JA and Selle F. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017; b18: 1274–1284.
19. Coleman RL, Oza AM and Lorusso D. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; 390: 1949–1961.
20. Penson RT, Valencia RV and Cibula D. Olaparib versus nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline BRCA1/2 mutation (SOLO3): a randomized phase III trial. *J Clin Oncol* 2020; 38: 1164–1174.
21. Kaufman B, Shapira-Frommer R, Schmutzler RK, *et al.* Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol* 2015; 33: 244–250.
22. Gelmon KA, Tischkowitz M, Mackay H, *et al.* Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol* 2011; 12: 852–861.
23. Moore KN, Secord AA, Geller MA, *et al.* Niraparib monotherapy for late-line treatment of

ovarian cancer (Quadra): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol* 2019; 20: 636–648.

24. Raymond E, Chaney SG, Taamma A, *et al.* Oxaliplatin: a review of preclinical and clinical studies. *Ann Oncol* 1998; 9: 1053–1071.
25. Piccart MJ, Green JA, Lacave AJ, *et al.* Oxaliplatin or paclitaxel in patients with platinum-pretreated advanced ovarian cancer: a randomized phase II study of the European Organization for research and treatment of Cancer Gynecology Group. *J Clin Oncol* 2000; 18: 1193–1202.
26. NCCN Clinical Practice Guidelines in Oncology. Ovarian Cancer/fallopian tube cancer/primary peritoneal cancer. Version I 2018.
27. Li X, Liu G and Wu W. Recent advances in Lynch syndrome. *Exp Hematol Oncol* 2021; 10: 37.
28. Nicoletto MO, Bertorelle R, Borgato L, *et al.* Family history of cancer rather than p53 status predicts efficacy of pegylated liposomal doxorubicin and oxaliplatin in relapsed ovarian cancer. *Int J Gynecol Cancer* 2009; 19: 1022–1028.
29. Schwartz LH, Litière S, de Vries E, *et al.* RECIST 1.1-Update and clarification: from the RECIST committee. *Eur J Cancer* 2016; 62: 132–137.
30. Cole SR and Hernán MA. Adjusted survival curves with inverse probability weights. *Comput Methods Programs Biomed* 2004; 75: 45–49.
31. R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, https://www.R-project.org/ (2021).
32. Nicoletto MO, Falci C, Pianalto D, *et al.* Phase II study of pegylated liposomal doxorubicin and oxaliplatin in relapsed advanced ovarian cancer. *Gynecol Oncol* 2006; 100: 318–323.
33. Poveda A, Floquet A, Ledermann JA, *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: 6002–6002.
34. Dieras V, Bougnoux P, Petit T, *et al.* Multicentre phase II study of oxaliplatin as a single-agent in cisplatin/carboplatin +/- taxane-pretreated ovarian cancer patients. *Ann Oncol* 2002; 13: 258–266.
35. Palma MD, Lombardi G, Donach ME, *et al.* Tolerability of PLD/oxaliplatin regimen in recurrent ovarian cancer patients with previous fragility to carboplatin/paclitaxel treatment. *Am J Clin Oncol Cancer Clin Trials* 2011; 34: 305–308.
36. Kaye SB, Lubinski J, Matulonis U, *et al.* Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. *J Clin Oncol* 2012; 30: 372–379.
37. Safra T, Borgato L, Nicoletto MO, *et al.* BRCA mutation status and determinant of outcome in women with recurrent epithelial ovarian cancer treated with pegylated liposomal doxorubicin. *Mol Cancer Ther* 2011; 10: 2000–2007.
38. Monk BJ, Herzog TJ, Kaye SB, *et al.* Trabectedin plus pegylated liposomal doxorubicin (PLD) versus PLD in recurrent ovarian cancer: overall survival analysis. *Eur J Cancer* 2012; 48: 2361–2368.
39. Cecere SC, Giannone G, Salutari V, *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.
40. Makrilia N, Syrigou E, Kaklamanos I, *et al.* Hypersensitivity reactions associated with platinum antineoplastic agents: a systematic review. *Met Based Drugs* 2010; 2010: 207084.