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Efficacy of a platinum-based chemotherapy rechallenge for platinum-sensitive recurrence after PARP inhibitor maintenance

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ABSTRACT

Objective: Platinum-free interval (PFI) is the period from the end of platinum-based chemotherapy to the date of recurrence. If the PFI is > 6 months, a platinum-based chemotherapy rechallenge is considered; however, its efficacy after poly adenosine 5′-diphosphate-ribose polymerase (PARP) inhibitor maintenance therapy is unknown. This study aimed to examine the efficacy of a platinum-based chemotherapy rechallenge after PARP inhibitor therapy.

Methods: We retrospectively evaluated patients with ovarian cancer with a PFI≥6 months with PARP inhibitor maintenance therapy, receiving platinum-based chemotherapy. Duration of PARP inhibitor therapy, best response to subsequent platinum chemotherapy rechallenge, and clinical characteristics were collected from medical records. Tumor response was assessed according to RECIST 1.1. Correlations were calculated using Spearman's correlation coefficients.

Results: Among the 10 included patients, seven (70 %) received PARP inhibitors after primary chemotherapy, and three (30 %) received chemotherapy for platinum-sensitive relapse. One and five patients harbored a germline *BRCA1* and *BRCA* wild-type mutations, respectively, and two had homologous recombination proficiency. The median PFI was 303.5 (182–602) days, and PARP inhibitor therapy duration was 249 (147–570) days. Platinum chemotherapy rechallenge efficacy was complete and partial response and stable disease in one (10 %), six (60 %), and three (30 %) patients, respectively. The longer the duration of PARP inhibitor treatment, better the response to platinum agents (Spearman correlation coefficient 0.284, $p = 0.0288$).

Conclusion: Platinum-based chemotherapy rechallenge is reasonable for patients with platinum-sensitive disease, using the traditional PFI cutoff of 6 months, even when the PFI is obtained with a maintenance PARP inhibitor.

1. Introduction

Ovarian cancer is the fifth leading cause of cancer-related death in women, with an estimated 313,959 new cases and 207,252 deaths reported worldwide in 2020 (Hyuna et al., 2021). Approximately 80 % of ovarian cancers are detected in advanced stages, with a 5-year survival rate of 49 % and a poor prognosis (Siegel, et al, 2019). Platinum-based chemotherapy is the standard treatment for ovarian cancer. Poly adenosine 5′-diphosphate-ribose polymerase (PARP) inhibitors can prolong survival outcomes when used as maintenance therapy in first-line and platinum-sensitive recurrent ovarian cancer, especially for patients with homologous recombination deficiency (HRD)-positive cancer or *BRCA1/2* mutations (Moore et al., 2018; Gonzalez-Martin et al., 2019; Ray-Coquard et al., 2019; Coleman et al., 2019; Miller et al., 2020; DiSilvestro et al., 2023; Ray-Coquard et al., 2023). However, the platinum-free interval (PFI) is considered a major criterion for predicting the efficacy of platinum-based chemotherapy in recurrent ovarian cancer. Moreover, in a previous report, the response rates to rechallenge with platinum-based chemotherapy were higher in patients with a longer PFI (Harries and Gore, 2002). PFI>6 months is classified as a

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platinum-sensitive recurrence, and platinum-based chemotherapy is rechallenged in general (Wilson et al., 2017). However, the efficacy of platinum rechallenge is unknown when patients receive PARP inhibitor maintenance therapy following platinum-based chemotherapy for > 6 months, although PFI may be "artificially" prolonged by PARP inhibitors. Therefore, this study aimed to investigate the correlation between PFI and the duration of PARP inhibitor maintenance therapy and the efficacy of platinum-based chemotherapy for platinum-sensitive recurrence in patients with ovarian cancer.

2. Materials and methods

2.1. Subjects

We retrospectively evaluated patients with ovarian, tubal, and peritoneal cancers who were treated with platinum-based chemotherapy and subsequent PARP inhibitor maintenance therapy between April 1, 2017, and December 31, 2021. We analyzed the efficacy and outcome of platinum rechallenge in patients who experienced recurrence despite continued PARP inhibitor maintenance therapy for > 6 months.

2.2. Data collection

The following clinical data were collected from electronic medical records: age, histology, clinical stage, germline *BRCA1/2* status tested by BRACAnalysis CDx® (Myriad genetics), HRD status tested by MyChoice® CDX (Myriad genetics), type of chemotherapy, dates of treatment initiation and last administration of chemotherapy, number of chemotherapy cycles, tumor response to chemotherapy, presence or absence of recurrence, date of recurrence, presence or absence of death, and date of death or last known survival. This study was approved by the Institutional Review Board of National Cancer Center Hospital East (IRB number 2017–431). Informed consent was obtained in the form of opt-out on the website. Those who rejected were excluded.

2.3. Statistical analysis

PFI was defined as the time between the last date of platinum-based chemotherapy before PARP inhibitor maintenance and the date of recurrence or progression. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Progression-free survival (PFS) was defined as the time from the start of rechallenge with platinum-based chemotherapy after PARP inhibitor therapy to the date of confirmed disease progression or death. Correlations between PFI or administration period of PARP inhibitor and change in tumor size were calculated using Spearman's correlation coefficient. All statistical analyses were performed using Microsoft Excel ver. 4.01 (Social Survey Research Information Co., Ltd.) (Wilson et al., 2017).

3. Results

In total, 47 patients received PARP maintenance therapy after platinum-based chemotherapy for primary or recurrent ovarian carcinoma. Among them, 11 patients with a PFI>6 months relapsed, i.e., platinum-sensitive relapse. One patient was not evaluated because they did not receive any further treatment. Ultimately, 10 patients underwent a platinum rechallenge. The patient characteristics are presented in Table 1. The median age was 64.5 (range 39–79). All patients were classified as having FIGO stage III or IV disease, among which 90 % had high-grade serous carcinoma. Either or both BRACAnalysis CDx®□ and MyChoice®□ were tested at the physician's choice. One patient had germline *BRCA1/2* mutation, five had somatic HRP. One had unknown somatic HRD status, but a confirmed germline *BRCA 1/2* wild type. Three were not tested for either. Seven patients received PARP inhibitor maintenance therapy for primary treatment and three patients received maintenance therapy for recurrence treatment. Responses to chemotherapy before PARP inhibitor therapy were complete response (CR) in six (60 %) patients and partial response (PR) in four (40 %) patients. The main metastatic sites of recurrence were lymph nodes (40 %), peritoneal dissemination (30 %), liver (20 %), and lung (10 %). The PARP inhibitors administered as maintenance therapy were olaparib in four (40 %) patients and niraparib in six (60 %) patients. The physician's choice determined the PARP inhibitor. No patients received olaparib in combination with bevacizumab. The median PFI was 303.5 (182–602) days, and the median duration of PARP inhibitor maintenance therapy was 249 (147–570) days.

The efficacy of platinum rechallenge after PARP maintenance

Table 1
Patient characteristics.

		n = 10
Age (years)	Age, median (range)	64.5 (39–79)
Stage (FIGO)	International FIGO stage	
	stage III	5 (50 %)
	stage IV	5 (50 %)
Genetic variation	Genetic variation	
	germline *BRCA 1/2* mutation	1 (10 %)
	HRP*	5 (50 %)
	unknown HRD† status / germline *BRCA 1/2* wild type	1 (10 %)
	not tested	3 (30 %)
Histrogical type	Histrogical type	
	High grade serous carcinoma	9 (90 %)
	Mucinous carcinoma	1 (10 %)
Primary or recurrent for primary PARP inhibitor	Primary or recurrent for primary PARP inhibitor	
	Primary	7 (70 %)
	recurrent	3 (30 %)
Chemotherapy befor PARP inhibitor	Chemotherapy befor PARP inhibitor	
	dose-dense TC‡	7 (70 %)
	triweekly TC	2 (20 %)
	weekly TC	1 (10 %)
Best response of platinum-based chemotehrapy	Responses of chemotherapy	
before PARPi	CR§	6 (60 %)
	PR¶	4 (40 %)
Main metastatic sites	Lymph node	4 (40 %)
	Peritoneal dissemination	3 (30 %)
	Liver	2 (20 %)
	Lung	1 (10 %)
Maintenance therapy	Maintenance therapy	
	Olaparib	4 (40 %)
	Niraparib	6 (60 %)

*Homologous recombination proficient. † Homologous recombination deficiency. ‡ Paclitaxel and carboplatin.
§Complete response. ¶ Partial response.

Table 2
The effect and prognosis of platinum-based chemotherapy.

Characteristics	n = 10
PFI, days (median, range)	303.5 (182–608)
PARP inhibitor administration period, days (median, range)	249 (147–570)
Chemotherapy after PARP inhibitor	
triweeklyTC	3 (30 %)
TC+Bevacizumab	4 (40 %)
weekly TC	1 (10 %)
GC	1 (10 %)
GC+Bevacizumab	1 (10 %)
Responses of chemotherapy	
CR	1 (10 %)
PR	6 (60 %)
SD	3 (30 %)
Tumor response, % (median, range)	38 (9–100)
Progression-Free Survival, days (median, range)	177 (51–588)

therapy is presented in Table 2. The chemotherapy regimens employed for platinum rechallenge were triweekly paclitaxel and carboplatin (TC) in (30 %) patients, TC plus bevacizumab in four (40 %) patients, weekly TC in one (10 %) patient, gemcitabine and carboplatin (GC) in one (10 %) patient, and GC+bevacizumab in one (10 %) patient.

The overall response rate (ORR) to platinum rechallenge was 70 %: CR in one (10 %) patient, PR in six (60 %) patients, and stable disease in three (30 %) patients. No patient progressed without a tumor response or stabilization. Waterfall plots of the changes from baseline are illustrated in Fig. 1, and the case series outcomes are presented in Table 3. Tumor response was achieved by platinum rechallenge, regardless of *BRCA1/2* mutational or HRD status.

The correlation between PFI and the percentage change in tumor size from baseline is shown in Fig. 1. The trend observed indicated that the longer the PFI, the better the response to platinum-based chemotherapy (Coefficient of Determination 0.3558, Spearman's rank correlation coefficient 0.644 [p = 0.0446]) in Fig. 2. The correlation between the administration period of PARP inhibitors and the percentage change in tumor size from baseline is shown in Fig. S1. The figure illustrates that the longer the administration period of PARP inhibitor, the better the response to platinum-based chemotherapy (Coefficient of Determination 0.4143, Spearman's rank correlation coefficient 0.643 [p = 0.0288]).

4. Discussion

This study investigated the efficacy of rechallenge with platinum-based chemotherapy after maintenance therapy with a PARP inhibitor and the correlation between PFI or the duration of PARP inhibitor maintenance therapy and the efficacy of platinum-based chemotherapy in patients with ovarian cancer. We found that the overall response rate (ORR) reached 70 % with platinum retreatment and that PFI was a predictor of platinum sensitivity, even when modified by PARP inhibitors.

In previous reports, platinum sensitivity was classified using 6 months PFI cutoff. However, the cut-off value was defined in the days before bevacizumab or PARP inhibitor maintenance therapy, both of which have been shown to prolong PFS and are the standard of care today (Moore et al., 2018; Gonzalez-Martin et al., 2019; Ray-Coquard et al., 2019; Ray-Coquard et al., 2019; Coleman et al., 2019; Burger et al., 2011; Perren et al., 2011). Therefore, the definition of platinum sensitivity based on the PFI in patients receiving PARP inhibitor maintenance therapy remains unclear. In this study, rechallenge with platinum-based chemotherapy was shown to be effective as long as PFI was ≥ 6 months even though the PFI was "artificially" prolonged by PARP inhibitor maintenance therapy. However, we found that the longer the PFI period, the more likely the tumor was to respond to platinum-based chemotherapy (Fig. 3 and Table 3). Similarly, a retrospective study showed that in patients with rechallenge using platinum-based chemotherapy after olaparib maintenance therapy, PFS was longer for patients with PFI≥12 months than for those with PFI 6–12 months (Nakazawa et al., 2022). Conversely, previous studies have

Table 3
Case series outcomes.

Case	Genetic variation	Administration period of PARP inhibitor (days)	PFI (days)	Change from baseline (%)	PFS (days)
1	HRP	178	280	−9	51
2	HRP	252	266	−25	83
3	HRP	319	417	−26	82
4	germline *BRCA 1/2* mutation	182	182	−30	463
5	unknown HRD status / germline *BRCA 1/2* wild type	246	327	−38	192
6	not tested	496	524	−38	577
7	not tested	344	369	−39	588
8	HRP	147	216	−47	162
9	not tested	210	252	−47	145
10	HRP	570	608	−100	224

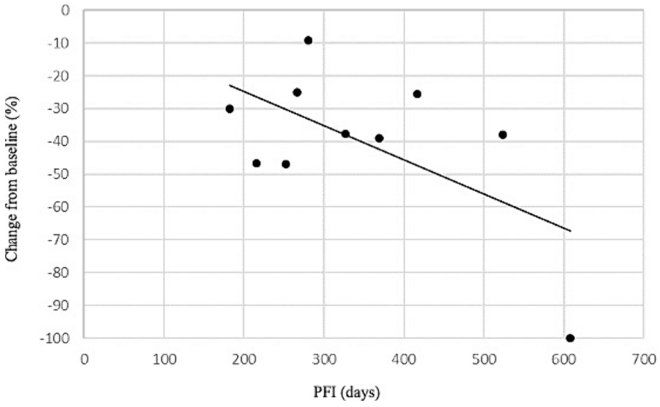

Fig. 2. Correlation between PFI and percent change in tumor size from baseline. Coefficient of Determination was 0.3558. Spearman's rank correlation coefficient was −0.644 (p = 0.0446).

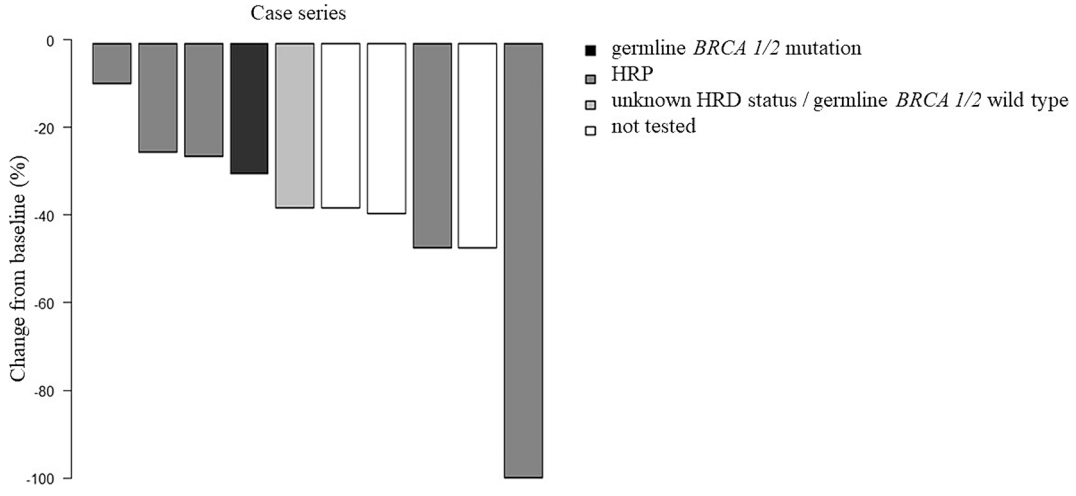

Fig. 1. Waterfall plots of tumor response.

indicated that the maintenance of PARP inhibitors may limit the efficacy of subsequent platinum rechallenge. For instance, second-line PARP inhibitor maintenance therapy is associated with a poor response to subsequent chemotherapy in *BRCA1/2*-mutated ovarian cancer (Frenel et al., 2022; Rose et al., 2021; Park et al., 2022). Although the mechanism of resistance to platinum agents is unclear, secondary mutations in *BRCA1/2* and *RAD51* are mechanisms of resistance to PARP inhibitors, which may potentially be common with resistance to platinum chemotherapy (Galluzzi et al., 2012; Damia and Broggini, 2019; Kondrashova et al., 2017). This study included patients who harbored *BRCA* mutations and were sensitive to platinum. However, due to the small limited size and several potential common mechanisms of resistance to PARP inhibitors and platinum drugs, we cannot deny the potential "carry over" resistance. Thus, further studies with serial molecular monitoring are required.

The limitations of this study include its single-center design, the small number of cases, and limited information on *BRCA1/2* and HRD. Moreover, 30 % of the patients did not undergo these genetic tests. This study cannot accurately discuss prognosis because it included and analyzed patients who received PARP inhibitors both upfront and at recurrent setting. Despite these limitations, this study suggests that platinum rechallenge may be effective in patients with PFI for $>$ 6 months, even if PFI is achieved with maintenance therapy using a PARP inhibitor, as a longer PFI correlates with a better response to platinum-based chemotherapy.

In conclusion, based on our finding that tumor response to platinum rechallenge was obtained after PARP inhibitor maintenance, even when adopting a traditional PFI cutoff of 6 months, there is no evidence to extend the cutoff to distinguish platinum-sensitive from platinum-resistant relapse. Given the potential cross-resistance to PARP inhibitors and platinum agents, individualization of platinum rechallenge according to molecular mechanisms should be developed in the future.

CRediT authorship contribution statement

Takehiro Nakao: Writing – original draft, Investigation. **Kenichi Harano:** Writing – review & editing, Supervision, Project administration, Methodology. **Masashi Wakabayashi:** Methodology, Formal analysis, Data curation. **Yoichi Naito:** Writing – review & editing. **Hiroshi Tanabe:** Writing – review & editing, Data curation. **Toru Mukohara:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics Approval

All study participants provided informed consent, and the study design was approved by the appropriate ethics review board. We have read and understood your journal's policies, and we believe that neither the manuscript nor the study violates any of these. There are no conflicts of interest to declare.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2024.101482.

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