

Efficacy and Safety of Platinum Rechallenge in Patients With Platinum-resistant Ovarian, Fallopian Tube or Primary Peritoneal Cancer: A Multicenter Retrospective Study

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Abstract. *Background/Aim:* Ovarian cancer diagnosed with platinum-resistant recurrence has very poor prognosis and single-agent chemotherapy with no cross-resistance to prior chemotherapy is recommended for its treatment. In this study, we retrospectively evaluated the efficacy and safety of platinum rechallenge therapy for once diagnosed with platinum-resistant ovarian cancer who had a platinum-free interval (PFI) of at least 6 months. *Patients and Methods:* The study included 49 patients who received platinum rechallenge therapy for ovarian, fallopian tube or primary peritoneal cancer who were once diagnosed with platinum-resistant recurrence between January 2010 and March 2021 and evaluated the efficacy and safety of this treatment. In addition, patient background factors were identified, and independent prognostic factors for progression-free survival (PFS) and overall survival (OS) were investigated. *Results:* A complete response was noted in 7 cases, partial response in 21, stable disease in 9, and progressive disease in 10. The response and disease control rates were 55% and 76%, respectively. The median PFS and OS were 8.5 months and 35.8 months, respectively. The independent prognostic factor was PFI for OS, and there was no independent prognostic factor for PFS. Seven patients discontinued chemotherapy owing to serious adverse events, including one patient with treatment-related death. *Conclusion:* Platinum rechallenge therapy for patients with platinum-resistant recurrence did not cause previously unreported adverse events, and the

adverse events were manageable. In addition, high response and disease control rates were observed, as well as long-term OS. Platinum rechallenge therapy for platinum-resistant ovarian cancer may be a viable treatment option.

The incidence of ovarian cancer is increasing annually. It is one of the most common gynecological malignancies, ranking third after cervical and uterine cancers. In 2020, there were 21,750 estimated new diagnoses of ovarian cancer and 13,940 deaths owing to the disease in the USA; deaths owing to ovarian cancer were higher than those owing to endometrial and cervical cancers (1). Paclitaxel and carboplatin (TC) therapy is the gold standard chemotherapy regimen for epithelial ovarian, fallopian tube, or primary peritoneal carcinoma based on clinical studies such as GOG111, OV-10, GOG158, and AGO trials (2-5). However, 25% of patients at first relapse experience platinum-resistance, and almost all patients who experience recurrence or progressive disease subsequently develop platinum-resistant disease (6). Single-agent chemotherapy with no cross-resistance to prior chemotherapy or best supportive care is recommended for platinum-resistant ovarian cancer (7, 8). The most common treatments for platinum-resistant ovarian cancer are pegylated liposomal doxorubicin (PLD), topotecan, paclitaxel, and gemcitabine (GEM) (9). However, overall response rates were no greater than 15%, and median progression-free survival (PFS) and median overall survival (OS) were only 3-4 months and 8-13 months respectively (10-12). Therefore, new treatments are required for platinum-resistant ovarian cancer. We previously reported a combination chemotherapy with no cross-resistance to prior chemotherapy for platinum-resistant ovarian cancer. In these reports, the PFS and OS were 2-7 months and 19 months, respectively, which were better than those of single-agent chemotherapy (13, 14).

We have been re-treating patients who were once diagnosed with platinum-resistant ovarian cancer and had a

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platinum-free interval (PFI) of ≥ 6 months with platinum rechallenge therapy. In this study, we retrospectively investigated the treatment results and discuss whether the treatment could be an option for platinum-resistant ovarian cancer.

Patients and Methods

Study approval and patients. This study was approved by the institutional review board of Iwate Medical University, School of Medicine (Approval No. MH2021-153). Platinum-resistant patients were defined as patients who relapsed within 6 months after the last platinum administration date. Therefore, patients who relapsed within 3 months or during treatment were also included in the definition of "platinum-resistant". In addition, PFI was defined as the time from last platinum administration to subsequent disease progression on radiographic assessment using the RECIST criteria.

Forty-nine patients once diagnosed with platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer and treated with platinum rechallenge therapy at the Department of Obstetrics and Gynecology, Iwate Medical University Hospital and Hachinohe Red Cross Hospital between January 1, 2010, and March 31, 2021, were included in the study. These patients were required to have a PFI for at least 6 months.

Treatment. Platinum rechallenge therapy was selected as TC therapy [paclitaxel dose of 175 mg/m² on day 1 and carboplatin at an area under the curve (AUC) of 5 on day 1, every 3 weeks], paclitaxel with cisplatin (TP) therapy (paclitaxel dose of 175 mg/m² on day 1 and cisplatin dose of 50 mg/m² on day 1, every 3 weeks), docetaxel with carboplatin (DC) therapy (docetaxel dose of 60 mg/m² on day 1 and carboplatin at an AUC of 5 on day 1, every 3 weeks). Other options included GEM with carboplatin (GC) therapy (GEM dose of 800 mg/m² on days 1 and 8, carboplatin at an AUC of 5 on day 1, every 3 weeks), PLD with carboplatin (PLDC) therapy (PLD dose of 30 mg/m² on day 1 and carboplatin at an AUC of 5 on day 1, every 4 weeks), CPT-11 with cisplatin (CPT-P) therapy (CPT-11 dose of 60 mg/m² on days 1, 8, and 15 plus cisplatin 60 mg/m² on day 1, every 4 weeks), and paclitaxel with nedaplatin therapy (paclitaxel dose of 175 mg/m² on day 1 and nedaplatin dose of 80 mg/m² on day 1, every 4 weeks). In the case of concomitant use of bevacizumab (BEV), 15 mg/kg was administered every 3 weeks according to the dosing criteria of our hospital, and treatment was continued until the occurrence of serious adverse events (AEs) that made it difficult to continue treatment or until disease progression.

Endpoints/variables. The primary endpoint was PFS, and the secondary endpoints were antitumor efficacy, AEs, and OS. Antitumor efficacy was assessed using the RECIST v1.1 (15) or the GCIG CA125 criteria (16). The incidence and severity of AEs and treatment-related AEs were evaluated according to the Common Toxicity Criteria for Adverse Events v4.0 JCOG Japanese version (CTCAE v4.0-JCOG) (17).

Statistical analysis. The data cutoff was set on September 30, 2021. PFS and OS were calculated from the date of the start of platinum rechallenge therapy to the documented date of progression, death, or last follow-up, whichever occurred first. The effect of survival was assessed by constructing Kaplan-Meier curves with a log-rank test.

Table I. Patient characteristics (N=49).

Age	
<60 years	24
≥ 60 years	25
PS	
0	44
1	5
Histological type	
Serous/Endometrioid	41
Clear/Mucinous	8
Number of prior regimens	
<4	17
≥ 4	32
BEV combined before platinum rechallenge	
Combined	33
Non-combined	16
Platinum-free interval	
<12 months	16
≥ 12 months	33
Platinum rechallenge regimens	
TC (+Bev)	24
TP (+Bev)	3
DC (+Bev)	7
GC (+Bev)	7
PLDC	4
CPT-P	3
PTX/NDP	1
Taxane combined in platinum rechallenge	
Combined	35
Non-combined	14
BEV combined in platinum rechallenge	
Combined	18
Non-combined	31
BEV combined after progression	
Combined	21
Non-combined	28
Anti-tumor evaluation	
RECIST ver1.1	47
GCIG CA125 criteria	2

PS, Performance status; TC, paclitaxel with carboplatin; TP, paclitaxel with cisplatin; DC, docetaxel with carboplatin; PLDC, doxorubicin with carboplatin; CPT-P, irinotecan with cisplatin; PTX/NDP, paclitaxel with nedaplatin; BEV, bevacizumab.

In addition, independent prognostic factors were investigated using univariate and multivariate analyses of eight factors: age, performance status (PS), histological type, number of previous regimens, PFI, concomitant use of taxane agent, concomitant use of BEV, and antitumor efficacy. Statistical analyses were performed using EZR (Easy R) version 1.54 (available on our website; <http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html>) with significance set at $p < 0.05$ (18).

Results

Patient characteristics. Table I summarizes the background factors of 49 patients enrolled in this study. The median age of the 49 patients was 59 years (range=35-84 years). The PS

Table II. Anti-tumor response (N=49).

	N	%
CR	7	14.3
PR	21	42.8
SD	9	18.4
PD	10	20.4
NE	2	4.1
Overall response	28	57.1
Disease control	37	75.5

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

was 0 in 44 patients (89.7%) and 1 in five patients (10.3%). The histological type was serous carcinoma in 40 patients (81.6%), mucinous carcinoma in three (6.1%), clear cell carcinoma in five (10.2%), and endometrioid carcinoma in one (2.0%). The number of prior regimens in 17 patients (34.7%) was <4 and in 32 patients (65.3%) was ≥ 4 . Thirty-three patients (67.3%) were administered BEV before this treatment, and 16 patients (32.7%) were treated without BEV. The PFI of the patients was <12 months in 16 patients (32.7%) and ≥ 12 months in 33 patients (67.3%).

The platinum rechallenge regimens administered to the enrolled patients were TC (with BEV) therapy to 24 patients (49.0%), TP (with BEV) therapy to 3 (6.1%), DC therapy to 7 (14.3%), GC (with BEV) therapy to 7 (14.3%), PLDC therapy to 4 (8.2%), CPT-P therapy to 3 (6.1%), and paclitaxel with nedaplatin therapy to one patient (2.0%). 35 patients (71.4%) were treated with taxane agents and 14 (28.6%) without taxane agents. 18 patients (36.7%) were treated with BEV and 31 (63.3%) without BEV.

21 patients (42.9%) were administered BEV after progression of these regimens and 28 patients (57.1%) were treated without BEV.

Antitumor response. Table II summarizes the antitumor effects observed in the 49 patients. The antitumor response was evaluated in 47 patients (95.9%) by the definition of RECIST v1.1 and in 2 patients (4.1%) by the GCIG CA125 criteria. Complete response was noted in 7 patients (14.3%), partial response in 21 (42.8%), stable disease in 9 (18.4%), progressive disease in 10 (20.4%), and no evaluation in 2 (4.1%). The objective response and disease control rates were 55% and 76%, respectively.

Survival analysis. Figure 1 shows the PFS and OS of all patients. The median follow-up period was 20 months (range=0-81 months), and the median PFS and OS were 8.5 months [95% confidence interval (CI)=6.5-12 months] and 35.8 months (95% CI=21.8-55 months), respectively.

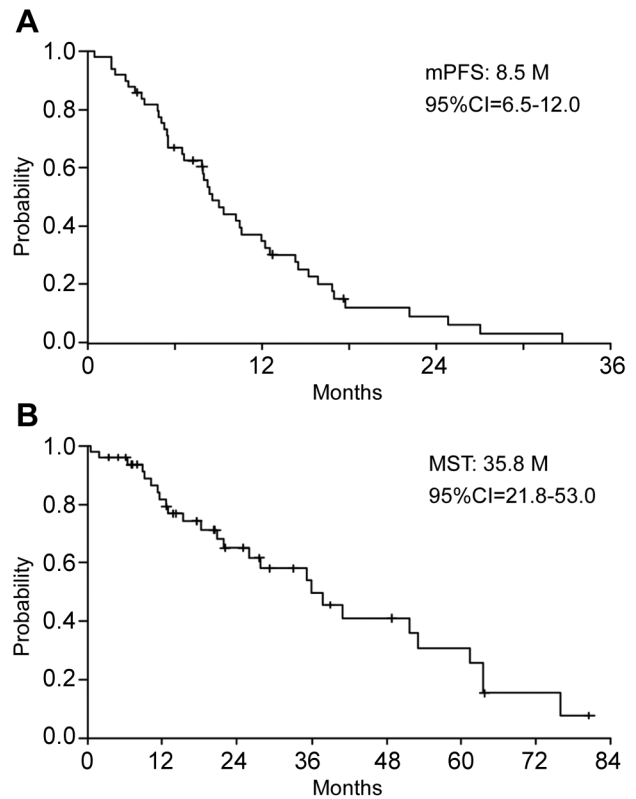


Figure 1. Kaplan-Meier curve for investigator-assessed progression-free survival (PFS) (A) and overall survival (OS) (B). The median PFS and OS were 8.5 months and 35.8 months, respectively. MST, Median survival time; CI, confidence interval.

We performed univariate and multivariate analyses of PFS and OS for background factors listed in Table I. No independent prognostic factor was found for PFS (Table III), and PFI was an independent prognostic factor for OS. PFI was classified into two groups: ≥ 12 months and <12 months (Table IV), and OS of each group was calculated and compared. The median OS of the groups with PFI ≥ 12 months and <12 months were 41 months and 21.8 months, respectively, with statistically significant differences [hazard ratio (HR)=0.34, 95% CI=0.14-0.83, $p=0.0128$] (Figure 2).

Adverse events. The AEs that developed in this study are presented in Table V. Grade 3 or higher hematologic toxicities included leukopenia in 31 patients (63.3%), neutropenia in 36 (73.5%), anemia in 13 (26.5%), and thrombocytopenia in 10 (20.4%). Febrile neutropenia occurred in 4 patients (8.2%). In contrast, non-hematological toxicities of grade 3 or higher were peripheral neuropathy, hypertension, and proteinuria in 1 patient (2.0%) and carboplatin hypersensitivity in 2 patients (4.1%).

Table III. Univariate and multivariate analyses of progression-free survival (PFS) for background. No independent prognostic factor was found for PFS.

PFS-Cox proportional hazard model (Univariate analysis)			
	Hazard ratio	95%CI	p-Value
Age (>T.60)	1.37	0.74-2.53	0.3078
PS (T.1)	1.92	0.67-5.53	0.223
Histology (T. Serous•Endometrioid)	0.5	0.21-1.17	0.1119
prior regimens (>T.4)	0.79	0.41-1.51	0.486
PFI (>T.12 months)	0.61	0.31-1.20	0.1582
Taxane agents (T. Combined)	1.02	0.51-2.05	0.9423
Bevacizumab (T. Combined)	0.89	0.48-1.67	0.7374
Tumor response (T.SD/PD/NE)	1.95	1.02-3.71	0.0419
PFS-Cox proportional hazard model (Multivariate analysis)			
	Hazard ratio	95%CI	p-Value
Age (>T.60)	1.39	0.72-2.68	0.315
PS (T.1)	2.1	0.68-6.51	0.195
Histology (T. Serous•Endometrioid)	0.58	0.20-1.66	0.316
Prior regimens (>T.4)	0.8	0.38-1.68	0.571
PFI (>T.12 months)	0.56	0.25-1.23	0.15
Taxane agent (T. Combined)	1.78	0.75-4.21	0.184
Bevacizumab (T. Combined)	0.97	0.45-2.10	0.953
Tumor response (T.SD/PD/NE)	1.76	0.77-4.02	0.178

HR, Hazard ratio; PS, performance status; PFI, platinum-free interval; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

Table IV. Univariate and multivariate analyses of overall survival (OS) for background. Platinum-free interval (PFI) was an independent prognostic factor for OS (HR=0.28, 95% CI=0.09-0.83, p=0.022).

OS-Cox proportional hazard model (Univariate analysis)			
	Hazard ratio	95%CI	p-Value
Age (>T.60)	0.99	0.45-2.16	0.989
PS (T.1)	0.95	0.12-7.29	0.964
Histology (T. Serous•Endometrioid)	0.39	0.15-1.03	0.058
Prior regimens (>T.4)	0.4	0.16-0.97	0.044*
PFI (>T.12 months)	0.34	0.14-0.82	0.016*
Taxane agent (T. Combined)	1.14	0.47-2.75	0.758
Bevacizumab (T. Combined)	1.07	0.48-2.38	0.85
Tumor response (T.SD/PD/NE)	2.12	0.96-4.68	0.062
OS-Cox proportional hazard model (Multivariate analysis)			
	Hazard ratio	95%CI	p-Value
Age (>T.60)	1.21	0.44-3.34	0.708
PS (T.1)	1.38	0.14-12.80	0.774
Histology (T. Serous•Endometrioid)	0.45	0.12-1.62	0.226
Prior regimens (>T.4)	0.5	0.16-1.51	0.221
PFI (>T.12 months)	0.28	0.09-0.83	0.022*
Taxane agent (T. Combined)	1.84	0.56-5.99	0.306
Bevacizumab (T. Combined)	1.38	0.43-4.35	0.58
Tumor response (T.SD/PD/NE)	2.32	0.78-6.88	0.128

HR, Hazard ratio; PS, performance status; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable. *p<0.05.

Table V. Adverse events.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥3
Hematologic toxicity					
Leucopenia	4	13	25	6	31 (63.3%)
Neutropenia	4	4	16	20	36 (73.5%)
Anemia	18	16	12	1	13 (26.5%)
Thrombocytopenia	21	7	7	3	10 (20.4%)
Febrile neutropenia	0	0	4	0	4 (8.2%)
Non-hematologic toxicity					
Nausea	20	2	0	0	0 (0.0%)
Neuropathy	19	8	1	0	1 (2.0%)
Diarrhea	2	0	0	0	0 (0.0%)
Constipation	8	1	0	0	0 (0.0%)
Hand foot syndrome	3	1	0	0	0 (0.0%)
Appetite loss	2	2	0	0	0 (0.0%)
Fatigue	13	4	0	0	0 (0.0%)
Hypertension	4	4	1	0	1 (2.0%)
Proteinuria	7	7	1	0	1 (2.0%)
CBDCA hypersensitivity	0	2	2	0	2 (4.1%)

CBDCA, Carboplatin.

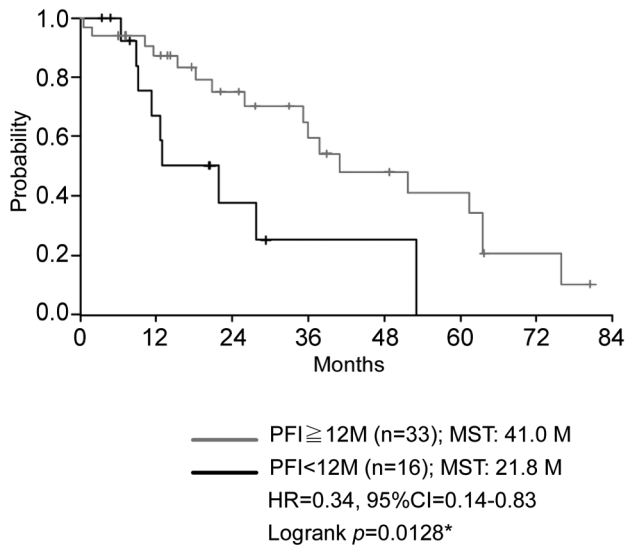


Figure 2. Kaplan-Meier curve comparing overall survival (OS) in PFI ≥ 12 months and < 12 months. The median OS of the groups with PFI ≥ 12 months and < 12 months were 41 months and 21.8 months, respectively, with statistically significant differences (HR=0.34, 95% CI=0.14-0.83, $p=0.0128$). PFI, Platinum-free interval; MST, median survival time; HR, hazard ratio; CI, confidence interval.

Seven patients (14.3%) had to discontinue treatment due to AEs. These seven patients included two patients on TC (with BEV) therapy (carboplatin hypersensitivity, gastrointestinal perforation), two on DC (with BEV) therapy (carboplatin hypersensitivity, grade 3 anemia), two on GC (with BEV) therapy (grade 4 thrombocytopenia, grade 4 anemia), and one on paclitaxel with nedaplatin therapy (grade 4 anemia). If carboplatin hypersensitivity was grade 2 or lower, desensitization therapy was administered according to our previously reported desensitization protocol (19). Desensitization therapy was administered to 2 patients (4.1%), which was 7.6% of 42 patients who received platinum rechallenge therapy with carboplatin. In this study, there was one treatment-related death, which was owing to gastrointestinal perforation (GIP) after TC + BEV therapy.

Discussion

There is a paucity of effective treatment options for patients with platinum-resistant ovarian cancer (20). There are few reports of platinum rechallenge therapy for platinum-resistant ovarian cancer. Havrilesky *et al.* reported a response rate of 37.5% in eight patients with platinum-resistant ovarian cancer treated with weekly low-dose carboplatin and paclitaxel (one cycle of carboplatin at an AUC of 2 and paclitaxel at 80 mg/m² on days 1, 8, and 15 for a 28-day cycle) (21). Hansen *et al.* reported a response rate of 57%

and PFS and OS of 5.0 months and 11.2 months, respectively, with carboplatin plus BEV in platinum-resistant ovarian cancer (one cycle of carboplatin at an AUC of 5 and BEV at 10 mg/kg on day 1 for a 21-day cycle) (22).

In our institution, platinum rechallenge therapy has been actively administered for the patients who were once diagnosed platinum-resistant ovarian cancer with PFI ≥ 6 months. In this study, we retrospectively investigated the efficacy and safety of this platinum rechallenge therapy and discussed its potential as a treatment option for platinum-resistant ovarian cancer.

The median OS of patients treated with single-agent chemotherapy for platinum-resistant ovarian cancer has been reported to be 8-13 months (9-12). In contrast, platinum combination therapy for platinum-sensitive ovarian cancer has been reported to result in an OS of 26.7-33.3 months (23-25). In the present study, the median OS of all 49 patients was 35.8 months, and among them, the median OS of 33 patients with PFI for ≥ 12 months was 41 months. OS is dependent on post-treatment, and median OS in the current study was better than median OS of platinum-resistant ovarian cancer cases reported previously (10-14). Proveda *et al.* reported that the results of the MITO-8 trial showed that extending PFI between 6 and 12 months with single-agent chemotherapy did not improve OS with subsequent platinum-based therapy, and in fact worsened outcomes (26-27). Our data in the present study contradict this report. It is difficult to directly compare the two studies as the patients in our study had platinum-resistant ovarian cancer while in MITO-8 they had platinum-sensitive ovarian cancer, which was a fundamentally different target population.

In the sub-analysis, after progression of platinum rechallenge therapy, 21 of 49 patients were administered BEV with the median OS of 51 months (95% CI=21-63 months) and longer than 12 months (95% CI=9-NA months) for the 28 patients who were not administered ($p=0.0026$). 4 out of these 21 patients were BEV naïve cases. For these reasons, we considered that BEV administration may be strongly associated with OS prolongation after platinum rechallenge therapy. Unfortunately, we do not have biomarker data for these patients, so we cannot explain exactly why the OS was prolonged in this study. Prospective multicenter trials comparing platinum rechallenge therapy with single-agent chemotherapy in platinum-resistant patients with concomitant DNA sequencing testing are needed to demonstrate the benefit of platinum rechallenge therapy.

We compared AEs of this study with those of previously reported chemotherapy regimens for platinum-sensitive ovarian cancer (23-25). Regarding hematological toxicity, leukopenia, and neutropenia of grade 3 or higher were observed in 31 (63.3%) and 36 (73.5%) patients, respectively. However, febrile neutropenia occurred in only 4 patients (8.2%). Similarly, anemia and thrombocytopenia

were observed in 13 (26.5%) and 10 (20.4%) patients, respectively. However, even if grade 3 or higher AEs developed, platinum rechallenge therapy was continued by administering granulocyte colony-stimulating factor preparations and blood transfusion. Only 3 patients (6.1%) discontinued treatment because of hematological toxicity. Regarding non-hematological toxicities, the frequency of the occurrence of grade 3 or higher AEs in each category was low, and no AEs specific to this study occurred.

In addition, one case of grade 5 AE was observed. This case was considered a treatment-related death because it occurred within 28 days of treatment. In this case, GIP occurred after TC with BEV therapy; thus, it is quite possible that the AE was caused by BEV. However, since the onset of the disease occurred on day 3 after the first cycle of administration, we could not rule out GIP owing to exacerbation of the primary disease. In this case, GIP occurred despite meeting the criteria for BEV administration at our hospital. We believe that it is necessary to reconsider the dosing criteria for BEV separately for initial and recurrent treatments.

No previously unreported AEs of platinum-based regimens were observed in this study. Although hematological toxicities tended to occur with high frequency, they were manageable. The incidence of non-hematological toxicities was similar compared previous reports (23-25). High response and disease control rates were noted, and OS was equal to or better than that of patients treated with chemotherapy for platinum-sensitive ovarian cancer. Therefore, platinum rechallenge therapy for platinum-resistant ovarian cancer with a PFI of at least 6 months may be a new treatment option.

Recently, the efficacy of cabazitaxel, a new taxane-based anticancer agent, for the treatment of platinum-resistant ovarian cancer was reported (28). The response rate by GCIG CA125 criteria was 46%, and the partial response rate by RECIST Criteria was 15%, median PFS and OS were 3.9 months (95% CI=1.9-4.4) and 8.4 months (95% CI=5.1-11.0) respectively. All patients were administered with prophylactic granulocyte colony-stimulating factor (G-CSF) and toxicity was manageable. Cabazitaxel also has the potential to be a treatment option for platinum-resistant ovarian cancer; we thought its ability to prolong PFS and OS may be limited.

This study had several limitations. First, this was a two-center retrospective study. Second, the study included patients who were once diagnosed as platinum resistant but had a PFI of at least 6 months. This means that this study was an analysis of the population that may benefit from a platinum agent. The type of chemotherapy that should be selected for patients with platinum-refractory recurrence should be investigated in future studies. Finally, we did not assess quality of life (QOL), although it is important to continue chemotherapy without decreasing QOL in recurrent treatments.

In conclusion, based on the study, platinum rechallenge therapy for platinum-resistant ovarian cancer was effective, and its adverse effects were manageable, making it possible to be considered as a new treatment option. Patients with a PFI >12 months are expected to have longer OS. We hope that this report will lead to a reconsideration of the definition and treatment of platinum-resistant recurrent ovarian cancer.

Conflicts of Interest

All Authors declare that there are no conflicts of interest.

Authors' Contributions

Conceptualization: Tatsuki S, Shoji T. Literature search: Tatsuki S, Abe M, Tomabechi H, Takatori E, Kaido Y, Nagasawa T, Kagabu M. Writing-original draft preparation: Tatsuki S. Writing-review and editing: Shoji T, Baba T, Aida T. All Authors have read and agreed to the published version of the manuscript.

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