Cumulative cytotoxic chemotherapy exposure after the introduction of PARP inhibitors in advanced high-grade serous tubo-ovarian and primary peritoneal carcinoma: A descriptive single-center historical cohort study

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Abstract. The present study aimed to describe real-world treatment patterns, cumulative exposure to cytotoxic chemotherapy, and exploratory survival outcomes before and after the clinical introduction of poly(ADP-ribose) polymerase (PARP) inhibitors in patients with stage III-IV high-grade serous ovarian, fallopian tube or primary peritoneal carcinoma. The medical records of patients with stage III-IV high-grade serous ovarian, fallopian tube or primary peritoneal carcinoma who received chemotherapy at Jichi Medical University Saitama Medical Center (Saitama, Japan) between January 2009 and August 2023 were retrospectively reviewed. The primary outcomes were the number of chemotherapy regimens and the cumulative number of cytotoxic chemotherapy cycles. Overall survival was evaluated as an exploratory secondary outcome. The final cohort included 86 patients, comprising 48 patients in the PARP inhibitor-untreated group and 38 patients in the PARP inhibitor-treated group. The groups exhibited differences in several baseline characteristics, including International Federation of Gynecology and Obstetrics stage, receipt of neoadjuvant chemotherapy and cytoreduction status. The cumulative number of cytotoxic chemotherapy cycles was significantly higher in the PARP inhibitor-untreated group than in the PARP inhibitor-treated group [median, 18.5 (range, 6-49) vs. 12.0 (range, 5-45); P=0.020], whereas the number of chemotherapy regimens did not differ significantly [median, 3 (range, 1-7) vs. 2 (range, 1-8); P=0.081]. Overall survival appeared to be longer in the PARP inhibitor-treated group; however, this finding should be interpreted with caution due to the retrospective historical design and baseline imbalances. In this descriptive single-center cohort restricted to advanced high-grade serous ovarian, fallopian tube or primary peritoneal carcinoma, the clinical introduction of PARP inhibitors was associated with lower cumulative exposure to cytotoxic chemotherapy. No causal inference regarding survival benefits could be made due to substantial treatment-selection bias and baseline imbalances.

Introduction

Prospective randomized trials of poly(ADP-ribose) polymerase (PARP) inhibitors as maintenance therapy for advanced ovarian cancer, particularly high-grade serous carcinoma, have yielded inconsistent results regarding overall survival; although some studies reported a survival benefit, others did not report such benefits (1-3). Several studies have suggested that overall survival outcomes may differ depending on the homologous recombination deficiency status (2,3). In addition, survival advantages have not been consistent for recurrent ovarian cancer.

In Japan, following the Study 19 trial, PARP inhibitors were approved as maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer, irrespective of the homologous recombination deficiency status (4-13). In the recurrent setting, olaparib has also been evaluated as an oral targeted treatment option, rather than cyclic intravenous cytotoxic chemotherapy, in comparison with conventional non-platinum chemotherapy for patients with platinum-sensitive relapsed ovarian cancer and a germline *BRCA1/2* mutation (5). In routine practice, PARP inhibitor maintenance therapy may impose a different type of treatment burden from repeated intravenous cytotoxic chemotherapy and may reduce patients' cumulative exposure to conventional cytotoxic agents. Moreover, the SOLO2 trial demonstrated improved progression-free survival and preserved health-related quality of life among patients treated with olaparib maintenance therapy (6).

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The total burden of cytotoxic chemotherapy is clinically relevant because patients with advanced ovarian cancer often receive multiple lines of treatment over the course of their disease. A reduction in the cumulative number of cytotoxic chemotherapy cycles may represent a measurable change in treatment burden, although it does not directly capture quality of life, toxicity, or patient-reported outcomes. Therefore, real-world analyses describing the number of chemotherapy regimens and cumulative cytotoxic chemotherapy exposure may provide complementary information to survival-focused clinical trials.

Several randomized trials allowed subsequent PARP inhibitor administration after progression in patients who were initially assigned to placebo or comparator arms, which could complicate the interpretation of overall survival differences (14,15). A historical cohort may describe treatment patterns before and after the clinical introduction of PARP inhibitors, but such a design is inherently non-randomized and is susceptible to treatment-selection bias, era effects, and baseline imbalances. In the present study, we aimed to describe real-world treatment patterns, the number of chemotherapy regimens received, cumulative exposure to cytotoxic chemotherapy, and exploratory survival outcomes in patients with stage III-IV high-grade serous ovarian, fallopian tube, or primary peritoneal carcinoma treated before and after the introduction of PARP inhibitors at a single institution. This study was not designed to establish a causal survival benefit of PARP inhibitors.

Materials and methods

Patient selection. This study was approved by the Institutional Review Board of Jichi Medical University, Saitama Medical Center (approval number: S25-062), and conducted according to the Declaration of Helsinki (2024). Because the present study was a retrospective review of existing records, the requirement for informed consent was waived by the institutional review board. The current study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (https://www.equator-network.org/reporting-guidelines/strobe/) guidelines. We retrospectively reviewed the medical records of patients with stage III-IV high-grade serous ovarian, fallopian tube, or primary peritoneal carcinoma who received chemotherapy between January 2009 and August 2023 at our institution. Patients were excluded if they had a history of other malignancies, borderline ovarian tumors, or non-epithelial ovarian cancer, had non-high-grade serous histology, or were younger than 20 years at diagnosis.

Data retrieval. The following variables were extracted: age at diagnosis, International Federation of Gynecology and Obstetrics (FIGO) stage, receipt of neoadjuvant chemotherapy, completeness of cytoreduction, bevacizumab use, PARP inhibitor use, timing of PARP inhibitor initiation, duration of PARP inhibitor therapy, number of chemotherapy regimens received, and cumulative number of cytotoxic chemotherapy cycles. Patients who received a PARP inhibitor at any time during their treatment course were classified into the PARP inhibitor-treated group, whereas those who never received a PARP inhibitor were classified into the PARP inhibitor-untreated group. The timing of PARP inhibitor initiation was categorized as frontline maintenance or later-line maintenance. The best documented response to first-line platinum-based treatment was assessed after the completion of first-line chemotherapy or immediately before maintenance therapy, based on medical records and imaging reports, and categorized as complete response, partial response, stable disease, or progressive disease. In the PARP inhibitor-treated group, the best documented response immediately before PARP inhibitor initiation was recorded separately for frontline and recurrent maintenance settings based on the medical records and imaging reports. Completeness of cytoreduction was categorized as complete cytoreduction when no macroscopic residual disease remained, optimal cytoreduction when residual disease was ≤1 cm, and suboptimal cytoreduction when residual disease was >1 cm. The number of chemotherapy regimens received was defined as the number of distinct cytotoxic chemotherapy regimens administered during the disease course. The cumulative number of cytotoxic chemotherapy cycles was defined as the total number of cycles of cytotoxic agents administered, regardless of changes in regimen. PARP inhibitor maintenance therapy was not considered a cytotoxic chemotherapy regimen or cycle. For patients who experienced recurrence after PARP inhibitor therapy, platinum sensitivity after progression was also recorded. Platinum sensitivity was defined as recurrence or progression occurring ≥6 months after the last dose of platinum-based chemotherapy, whereas platinum resistance was defined as recurrence or progression occurring <6 months after the last dose of platinum-based chemotherapy.

Treatment strategy. First-line treatment generally consisted of paclitaxel plus carboplatin, with either primary debulking surgery or neoadjuvant chemotherapy followed by interval debulking surgery selected according to disease extent, resectability, and patient condition. Bevacizumab was used according to its approval and reimbursement status in Japan and the treating physician's judgment. At recurrence, platinum-based chemotherapy was generally selected for platinum-sensitive disease, whereas non-platinum chemotherapy was selected for platinum-resistant disease. PARP inhibitors were administered as maintenance therapy after response to platinum-based chemotherapy in eligible patients according to approval and reimbursement criteria in Japan.

Primary and secondary outcomes. The primary outcomes were the number of chemotherapy regimens received and the cumulative number of cytotoxic chemotherapy cycles. Overall survival was evaluated as an exploratory secondary outcome and was defined as the time from the initiation of first-line treatment to death from any cause. Survivors at the time of the last follow-up were censored at the most recent evaluation. Among patients who experienced recurrence after PARP inhibitor therapy, post-progression overall survival was defined as the time from recurrence or progression after PARP inhibitor therapy to death from any cause.

Statistical analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows version 26.0 (IBM

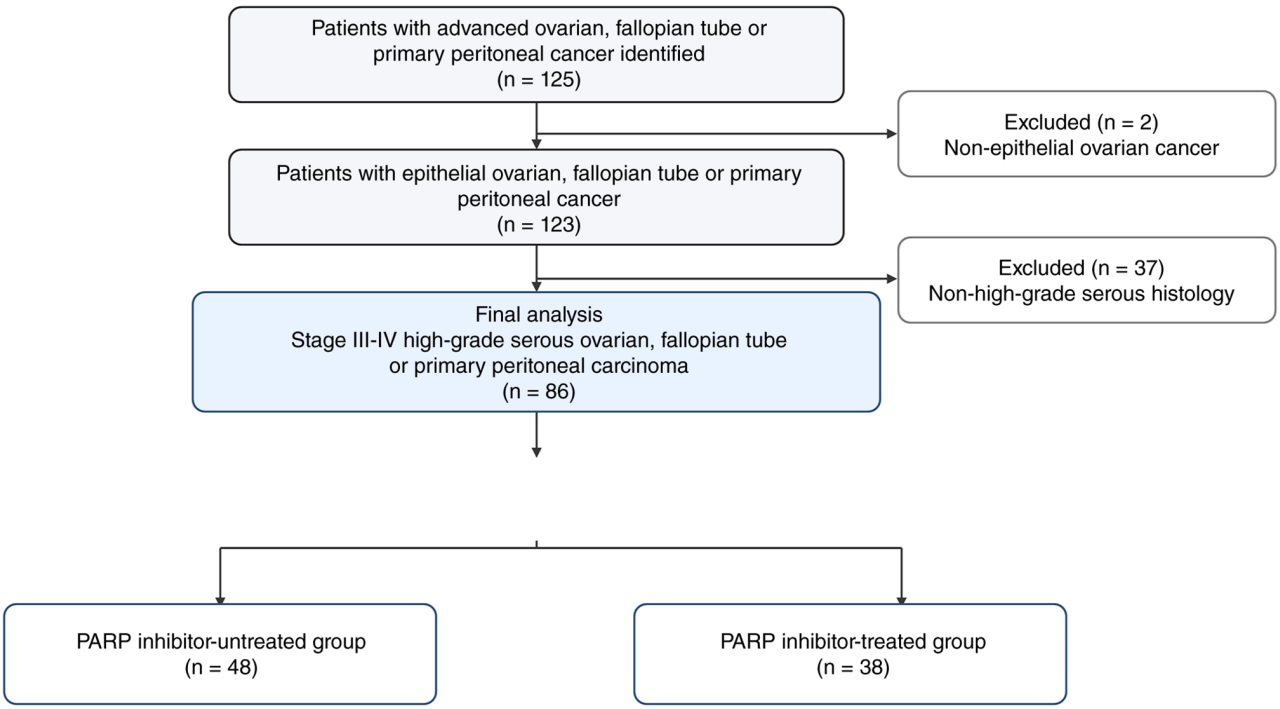

Figure 1. Flow diagram of patient selection. PARP, poly(ADP-ribose) polymerase.

Corp., Armonk, NY, USA). Follow-up duration was defined as the time from the initiation of first-line treatment to death or last follow-up. Continuous variables are presented as mean ± standard deviation or median (range), as appropriate. Normality of continuous variables was assessed using the Shapiro-Wilk test and by visual inspection of histograms and Q-Q plots. Normally distributed variables were compared using the unpaired Student's t-test, whereas non-normally distributed variables were compared using the Wilcoxon rank-sum test. Associations between categorical variables were assessed using Fisher's exact test. Overall survival was estimated using the Kaplan-Meier method. An unrestricted Kaplan-Meier analysis was initially inspected to assess the overall curve pattern; however, because late crossover of the survival curves was observed, this unrestricted analysis was not presented as a separate result. The between-group comparison presented in the Results section and Fig. 2 was based on a time-restricted log-rank analysis with administrative censoring at 110 months, before the observed late crossover. For this analysis, patients who were alive or who died after 110 months were censored at 110 months. To adjust for potential prognostic factors in the main cohort, multivariable Cox regression analysis for overall survival was performed using the same 110-month administrative censoring as the time-restricted log-rank analysis. The proportional hazards assumption for this model was assessed by testing time-dependent interactions between each covariate and log-transformed analysis time using the internal time variable in SPSS. The initial model included clinically relevant variables, including PARP inhibitor use, FIGO stage (stage IV vs. stage III), receipt of neoadjuvant chemotherapy, suboptimal cytoreduction, and bevacizumab use. Because bevacizumab use showed a significant time-dependent interaction with log-transformed analysis time, the final multivariable Cox regression model was stratified by bevacizumab use and included PARP inhibitor use, FIGO stage, receipt of neoadjuvant chemotherapy, and suboptimal cytoreduction as covariates. For the subgroup of patients who experienced recurrence or progression after PARP inhibitor therapy, post-progression overall survival was analyzed using Kaplan-Meier analysis and univariable Cox regression. Owing to the small number of patients in this subgroup, univariable Cox regression was used as the primary Cox regression approach to reduce the risk of overfitting. Exploratory multivariable Cox regression analysis was additionally performed. Because of the retrospective historical design and baseline imbalances between groups, survival analyses were considered exploratory and were not intended to establish causal effects of PARP inhibitors. All variables included in the primary analysis were available for all patients; therefore, no imputation was performed. Comprehensive BRCA mutation and homologous recombination deficiency data were not available for the full cohort and were therefore not included in the statistical models. Statistical significance was defined as a two-sided P-value of <0.05.

Results

Patient characteristics. During the study period, 125 patients with advanced ovarian, fallopian tube, or primary peritoneal cancer were identified. After excluding two patients with non-epithelial ovarian cancer and 37 patients with non-high-grade serous histology, 86 patients with stage III-IV high-grade serous carcinoma were included in the final analysis (Fig. 1). Of these, 48 patients were classified into the PARP inhibitor-untreated group and 38 into the PARP inhibitor-treated group.

Patient baseline characteristics are summarized in Table I. Age was similar between the two groups. However, baseline

Table I. Patient characteristics.

Variables	PARP inhibitor-untreated (n=48)	PARP inhibitor-treated (n=38)	P-value
Mean age ± SD, years	58.8±10.1	59.3±10.7	0.834
Stage, n (%)			0.012[a]
IIIA	0 (0.0)	3 (7.9)	
IIIB	1 (2.1)	7 (18.4)	
IIIC	38 (79.2)	22 (57.9)	
IVA	6 (12.5)	2 (5.3)	
IVB	3 (6.3)	4 (10.5)	
Neoadjuvant chemotherapy, n (%)	14 (29.2)	20 (52.6)	0.045[a]
Cytoreduction, n (%)			<0.001[a]
Complete	5 (10.4)	9 (23.7)	
Optimal	9 (18.8)	18 (47.4)	
Suboptimal	34 (70.8)	11 (28.9)	
Response to first-line platinum-based treatment, n (%)			0.212
Complete response	31 (64.6)	27 (71.1)	
Partial response	10 (20.8)	10 (26.3)	
Stable disease	2 (4.2)	1 (2.6)	
Progressive disease	5 (10.4)	0 (0.0)	
Bevacizumab use, n (%)	27 (56.3)	29 (76.3)	0.069
PARP inhibitor for frontline treatment, n (%)	-	20 (52.6)	
PARP inhibitor type, n (%)			
Olaparib	-	25 (65.8)	
Niraparib	-	13 (34.2)	
Median total number of regimens (range)	3 (1-7)	2 (1-8)	0.081
Median total cycles of cytotoxic chemotherapy (range)	18.5 (6-49)	12.0 (5-45)	0.020[a]

[a]Statistically significant difference. PARP, poly(ADP-ribose) polymerase.

imbalances remained in the FIGO stage, receipt of neoadjuvant chemotherapy, and cytoreduction status. Follow-up duration was 45 months (range, 14-156 months) in the PARP inhibitor-untreated group and 50.5 months (range, 22-144 months) in the PARP inhibitor-treated group. Neoadjuvant chemotherapy was more frequently used in the PARP inhibitor-treated group than in the PARP inhibitor-untreated group (52.6% vs. 29.2%, P=0.045). Suboptimal cytoreduction was more common in the PARP inhibitor-untreated group than in the PARP inhibitor-treated group (70.8% vs. 28.9%, P<0.001). The distribution of best documented response to first-line platinum-based treatment did not differ significantly between the groups (P=0.212). Complete and partial responses were observed in 31 (64.6%) and 10 (20.8%) patients, respectively, in the PARP inhibitor-untreated group, and in 27 (71.1%) and 10 (26.3%) patients, respectively, in the PARP inhibitor-treated group. Bevacizumab use was numerically more frequent in the PARP inhibitor-treated group, although the difference was not significant (76.3% vs. 56.3%, P=0.069). Among the 38 patients in the PARP inhibitor-treated group, 25 (65.8%) received olaparib and 13 (34.2%) received niraparib. PARP inhibitors were initiated as frontline maintenance therapy in 20 patients (52.6%) and as maintenance therapy in the recurrent setting in 18 patients (47.4%). The median duration of PARP inhibitor therapy was similar between the frontline (24 months, range: 10-55 months) and recurrent (23 months, range: 2-73 months) maintenance settings. Among patients who received PARP inhibitors as frontline maintenance therapy, the best documented response before PARP inhibitor initiation was a complete response in 13 patients (65.0%) and partial response in seven patients (35.0%). Among those who received PARP inhibitors as maintenance therapy in the recurrent setting, the best documented response before PARP inhibitor initiation was a complete response in four patients (22.2%), partial response in 13 patients (72.2%), and stable disease in one patient (5.6%).

Cytotoxic chemotherapy exposure. The cumulative number of cytotoxic chemotherapy cycles was significantly greater in the PARP inhibitor-untreated group than in the PARP inhibitor-treated group (median 18.5 (range, 6-49) vs. 12.0 (range, 5-45), P=0.020). In contrast, the number of chemotherapy regimens did not differ significantly between the groups (3 (1-7) vs. 2 (1-8), P=0.081).

Overall survival. Overall survival outcomes are shown in Fig. 2. Because late crossover of the Kaplan-Meier curves was observed in the overall survival analysis, a time-restricted

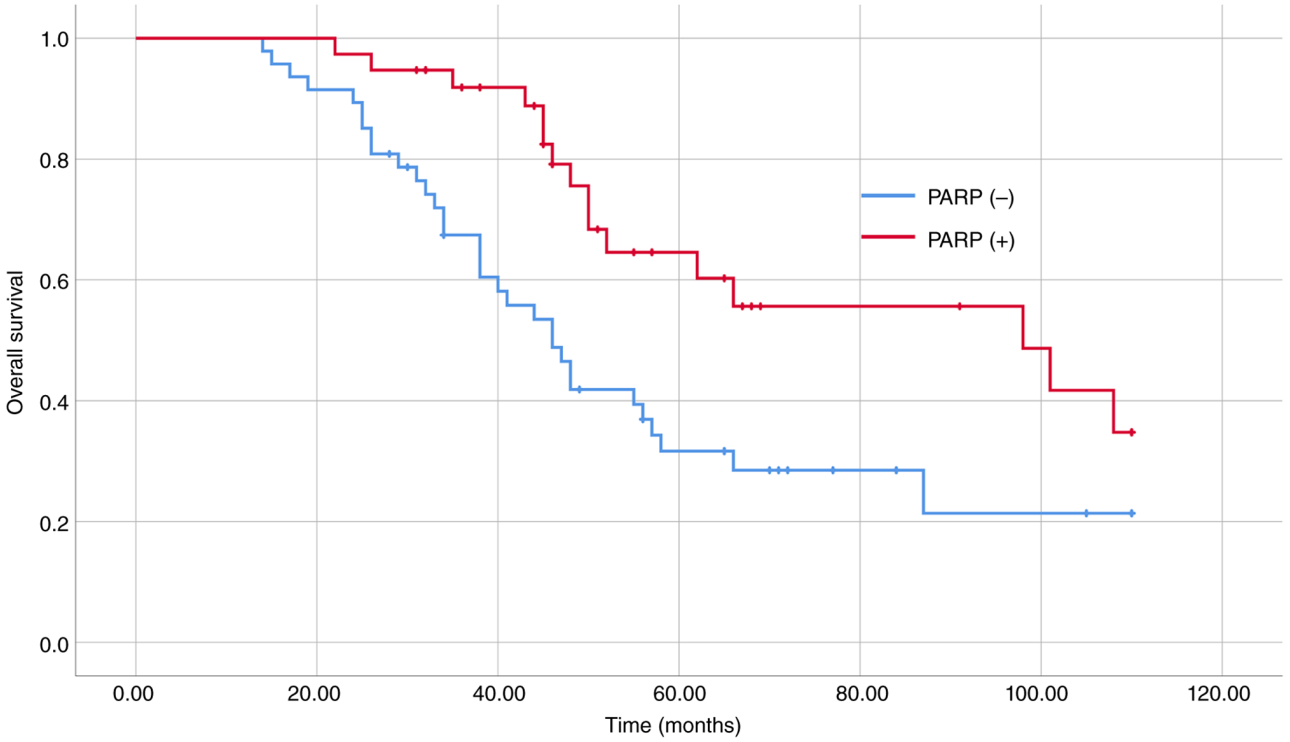

Figure 2. Kaplan-Meier curves for overall survival according to PARP inhibitor use, restricted to 110 months to exclude late crossover of the survival curves. The 5-year survival rate and median survival time in the PARP inhibitor-untreated group were 31.7% and 46 months, respectively, compared with 64.6% and 98 months, respectively, in the PARP inhibitor-treated group (P=0.011). Tick marks indicate censored observations. PARP, poly(ADP-ribose) polymerase.

log-rank analysis was additionally performed by administratively censoring observations at 110 months, before the observed late crossover of the survival curves. In this restricted analysis, the 5-year overall survival rate and median overall survival time in the PARP inhibitor-untreated group were 31.7% and 46 months, respectively, compared with 64.6% and 98 months, respectively, in the PARP inhibitor-treated group (P=0.011). The proportional hazards assumption was assessed for the time-restricted Cox regression model. No significant time-dependent interaction was observed for PARP inhibitor use, FIGO stage IV disease, suboptimal cytoreduction, or receipt of neoadjuvant chemotherapy. However, bevacizumab use showed a significant time-dependent interaction with log-transformed analysis time. Therefore, the final multivariable Cox regression model was stratified by bevacizumab use. In this stratified Cox regression analysis restricted to 110 months, PARP inhibitor use was associated with overall survival (HR, 0.400; 95% CI, 0.208-0.771; P=0.006). Receipt of neoadjuvant chemotherapy was also associated with overall survival (HR, 2.374; 95% CI, 1.246-4.523; P=0.009), whereas FIGO stage IV disease and suboptimal cytoreduction were not significantly associated with overall survival (Table II). These survival analyses were exploratory because of the retrospective historical design and baseline imbalances between the groups.

In the PARP inhibitor-treated group, multivariable Cox regression analysis revealed no significant prognostic factors for overall survival, including late-line PARP inhibitor initiation, bevacizumab use, FIGO stage IV disease, suboptimal cytoreduction, and receipt of neoadjuvant chemotherapy (Table III).

Post-progression overall survival after PARP inhibitor therapy. Recurrence or progression after PARP inhibitor therapy occurred in 26 patients, of whom 16 (61.5%) were classified as having platinum-sensitive disease. Patients with platinum-sensitive disease after progression had significantly longer post-progression overall survival than those with platinum-resistant disease (median, 21 vs. 5 months; P<0.001; Fig. 3). Because of the small number of patients in this subgroup, the primary analysis for post-progression overall survival was limited to univariable Cox regression to reduce the risk of overfitting. In the univariable Cox regression analysis, platinum sensitivity after progression was associated with longer post-progression overall survival (HR, 0.191; 95% CI, 0.068-0.538; P=0.002; Table IV). The results of the exploratory multivariable Cox regression analysis are shown in Table SI.

Discussion

In this descriptive single-center historical cohort restricted to patients with stage III-IV high-grade serous ovarian, fallopian tube, or primary peritoneal carcinoma, the clinical introduction of PARP inhibitors was associated with lower cumulative exposure to cytotoxic chemotherapy. The cumulative number of cytotoxic chemotherapy cycles was significantly lower in the PARP inhibitor-treated group than in the PARP inhibitor-untreated group, whereas the number of chemotherapy regimens did not differ significantly between the groups. Overall survival appeared longer in the PARP inhibitor-treated group; however, this finding should be interpreted as exploratory because of the retrospective historical design,

Table II. Multivariate Cox regression analysis for overall survival.

Variables	HR	95% CI	P-value
PARP inhibitor use	0.400	0.208-0.771	0.006[a]
FIGO stage IV (reference: Stage III)	1.540	0.783-3.031	0.211
Suboptimal cytoreduction	1.429	0.892-2.291	0.138
Neoadjuvant chemotherapy	2.374	1.246-4.523	0.009[a]
Bevacizumab use	Stratification variable		

[a]Significant association. The Cox regression model was restricted to 110 months and stratified by bevacizumab use because bevacizumab use showed a significant time-dependent interaction with log-transformed analysis time, as assessed by testing a time-dependent interaction term between each covariate and log-transformed analysis time using the internal time variable in SPSS. HR, hazard ratio; FIGO, International Federation of Gynecology and Obstetrics; PARP, poly(ADP-ribose) polymerase.

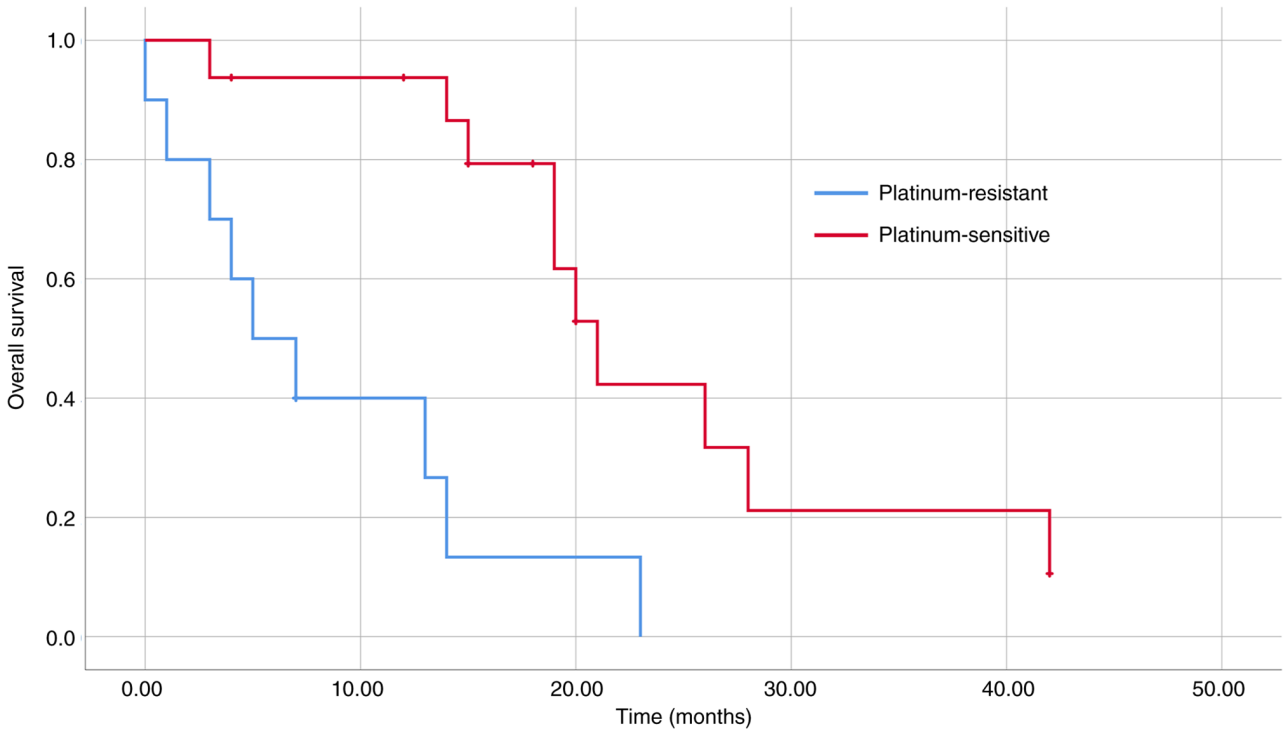

Figure 3. Kaplan-Meier curves for post-progression overall survival from the time of recurrence or progression after poly(ADP-ribose) polymerase inhibitor therapy. The median post-progression overall survival was significantly longer among patients with platinum-sensitive disease than among those with platinum-resistant disease (21 vs. 5 months; P<0.001). Tick marks indicate censored observations.

treatment-selection bias, era effects, and baseline imbalances between the groups.

This endpoint was selected as an objective measure of cytotoxic treatment exposure that could be consistently retrieved from medical records. Patients with advanced high-grade serous ovarian carcinoma often receive multiple lines of systemic treatment over the course of their disease, and repeated exposure to cytotoxic agents may contribute to treatment burden. PARP inhibitor maintenance therapy has been shown to prolong progression-free survival in pivotal trials, and health-related quality of life analyses have suggested that maintenance therapy can delay disease progression without a major deterioration in patient-reported outcomes (1-3,6). In this context, the lower cumulative number of cytotoxic chemotherapy cycles observed in the PARP inhibitor-treated group may represent a measurable change in real-world treatment patterns after the introduction of PARP inhibitor maintenance therapy. However, this finding should not be interpreted as direct evidence of improved quality of life or reduced toxicity, because patient-reported outcomes and treatment-related adverse events were not systematically evaluated in this retrospective analysis. Instead, cumulative cytotoxic chemotherapy cycles should be regarded as a surrogate measure of treatment exposure rather than a validated measure of patient burden. The number of chemotherapy regimens did not differ significantly between the two groups, suggesting that PARP inhibitor introduction may alter cumulative cytotoxic exposure without necessarily reducing the number of treatment lines.

Pivotal trials have demonstrated progression-free survival benefits of PARP inhibitor maintenance therapy,

Table III. Multivariate Cox regression analysis for the overall survival of patients treated with PARP inhibitors.

Variables	HR	95% CI	P-value
PARP inhibitor as a late-line treatment	0.445	0.128-1.542	0.202
Bevacizumab use	1.641	0.396-6.807	0.495
FIGO stage IV (reference: Stage III)	1.945	0.539-7.022	0.310
Suboptimal cytoreduction	0.813	0.382-1.729	0.591
Neoadjuvant chemotherapy	1.880	0.519-6.811	0.337

HR, hazard ratio; FIGO, International Federation of Gynecology and Obstetrics; PARP, poly(ADP-ribose) polymerase.

Table IV. Univariate Cox regression analysis for post-progression overall survival among patients experiencing recurrence or progression after PARP inhibitor therapy.

Variables	HR	95% CI	P-value
Platinum sensitivity after progression following PARP inhibitor use	0.191	0.068-0.538	0.002[a]
Bevacizumab use after progression	0.754	0.293-1.942	0.559
FIGO stage IV (reference: Stage III)	2.229	0.820-6.063	0.116
Suboptimal cytoreduction	0.589	0.336-1.034	0.065
Neoadjuvant chemotherapy	1.524	0.594-3.912	0.381

[a]Significant association. HR, hazard ratio; FIGO, International Federation of Gynecology and Obstetrics; PARP, poly(ADP-ribose) polymerase.

whereas overall survival benefits have been inconsistent and appear to vary according to BRCA mutation status, homologous recombination deficiency status, treatment line, and subsequent therapies (1-3). In the recurrent setting, the ENGOT-OV16/NOVA, ARIEL3, ARIEL4, SOLO3, QUADRA, and OReO trials highlighted the complexity of evaluating survival outcomes and subsequent treatment strategies after PARP inhibitor exposure (7-10,14,15). Unlike randomized trials, however, the present historical cohort study could not control for treatment indication, supportive care, surgical strategy, or era-related factors.

Although the analysis was restricted to high-grade serous carcinoma to reduce histologic heterogeneity, important baseline imbalances remained. The FIGO stage, use of neoadjuvant chemotherapy, and cytoreduction status differed between the groups. Suboptimal cytoreduction was more frequent in the PARP inhibitor-untreated group, whereas neoadjuvant chemotherapy was more frequent in the PARP inhibitor-treated group. These differences likely reflect changes in treatment strategy over time and differences in patient selection. Therefore, the observed survival association in the stratified multivariable Cox model should not be interpreted as causal evidence that PARP inhibitors improve overall survival in this cohort. It should be regarded as hypothesis-generating rather than confirmatory. Although multivariable Cox regression analysis was performed using clinically relevant prognostic factors, statistical adjustment could not fully account for residual confounding, treatment-selection bias, or unmeasured factors in this historical cohort.

The association between neoadjuvant chemotherapy and poorer overall survival should be interpreted as confounding by indication, because neoadjuvant chemotherapy is generally selected for patients with greater tumor burden, more extensive disease, poorer resectability, or reduced suitability for primary debulking surgery. Similarly, bevacizumab use was more frequent in the PARP inhibitor-treated group, likely influenced by disease extent, reimbursement status, and physician judgment.

In the exploratory analysis of patients who experienced recurrence or progression after PARP inhibitor therapy, platinum sensitivity after progression was associated with longer post-progression overall survival. However, because this subgroup included only 26 patients, the analysis was underpowered and vulnerable to statistical instability. Therefore, this finding should be interpreted as descriptive and hypothesis-generating. Previous studies have reported that prior PARP inhibitor exposure may influence response to subsequent chemotherapy, supporting the clinical importance of treatment sequencing after PARP inhibitor therapy (11,12). As new agents such as antibody-drug conjugates are being incorporated into the treatment landscape for platinum-resistant ovarian cancer, understanding post-PARP treatment sensitivity, sequencing, and biomarker-guided treatment selection remains clinically important (16).

This study has some limitations. First, this was a retrospective single-center historical cohort study with substantial treatment-selection bias and era effects; therefore, causal inference regarding the effect of PARP inhibitors

on overall survival could not be made. Second, although the cohort was restricted to high-grade serous carcinoma, baseline imbalances remained, particularly in FIGO stage, neoadjuvant chemotherapy, and cytoreduction status. In addition, immortal time bias may have affected the survival analysis, as patients in the PARP inhibitor-treated group had to survive and achieve disease control after platinum-based chemotherapy before receiving PARP inhibitor maintenance therapy. Although we added the response to first-line platinum-based treatment and the response immediately before PARP inhibitor initiation, this bias could not be eliminated in the retrospective design. Third, comprehensive *BRCA* mutation status and homologous recombination deficiency data were unavailable for the full cohort. Many patients had been treated before routine *BRCA*/HRD testing became available, and some had died by the time of this retrospective analysis; therefore, comprehensive post hoc biomarker testing was not feasible. Because *BRCA* and HRD status are closely associated with PARP inhibitor benefit, residual confounding by unmeasured biological factors cannot be excluded (1-3). Fourth, approximately half of the patients in the PARP inhibitor-treated group received PARP inhibitors as later-line maintenance therapy, which complicated the interpretation of survival outcomes and treatment exposure. Fifth, quality of life, adverse events, dose reductions, treatment interruptions, and hospitalization were not systematically evaluated in this retrospective analysis. These variables were not evaluated because patient-reported outcomes were not routinely collected, and treatment-related adverse events were not consistently recorded using standardized grading criteria throughout the long study period. In addition, the reasons for dose reductions and treatment interruptions were heterogeneous and could not be reliably classified retrospectively. Hospitalizations were also difficult to interpret as a surrogate for treatment burden or toxicity, because planned admissions for chemotherapy administration, admissions based on patient preference or social factors, disease-related admissions, and adverse-event-related admissions could not be consistently distinguished from medical records. Including these incompletely and inconsistently documented variables could have introduced substantial missing data and misclassification bias. Therefore, the lower cumulative number of cytotoxic chemotherapy cycles should not be interpreted as direct evidence of reduced toxicity or improved quality of life. Sixth, the subgroup analysis of post-progression overall survival after PARP inhibitor therapy included only 26 patients. To reduce the risk of overfitting, the main Cox regression analysis in this subgroup was limited to univariable analysis, and the multivariable model was presented only as an exploratory supplementary analysis. Therefore, the association between platinum sensitivity after progression and post-progression overall survival should be interpreted as descriptive and hypothesis-generating. Finally, differences in follow-up duration may have influenced cumulative cytotoxic chemotherapy exposure and exploratory survival outcomes, and may partly reflect differences in survival because follow-up duration was defined as the time from first-line treatment initiation to death or last follow-up.

In conclusion, this descriptive single-center cohort study restricted to advanced high-grade serous carcinoma suggests that the clinical introduction of PARP inhibitors was associated with lower cumulative exposure to cytotoxic chemotherapy. However, the number of chemotherapy regimens did not differ significantly between the groups, and no causal inference regarding a survival benefit could be made. Platinum sensitivity after recurrence or progression following PARP inhibitor therapy remained associated with post-progression survival in the exploratory analysis. Larger multicenter studies with biomarker data, toxicity data, and patient-reported outcomes are needed to clarify how PARP inhibitors influence long-term treatment burden and subsequent treatment sequencing in real-world practice.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

NO acquired clinical data from the medical records, performed the statistical analyses, investigated the treatment courses, and reviewed, edited and revised the manuscript. KC conceived and designed the study, developed the analytical approach, interpreted the data, wrote the original draft, and was involved in correspondence. KI acquired clinical data from the medical records and checked the extracted data against the source medical records. AS acquired clinical data and reviewed key clinical variables for accuracy. HK acquired clinical data and reviewed key clinical variables for accuracy. TK contributed to the interpretation of the clinical findings, supervised the study, and critically revised the manuscript for important intellectual content. NO and KC confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of Jichi Medical University, Saitama Medical Center (approval no. S25-062; Saitama, Japan). As this was a retrospective review of existing records, the requirement for informed consent was waived by this institutional review board.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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