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Original Article

Real world effectiveness and safety of pegylated liposomal doxorubicin in platinum-sensitive recurrent ovarian, fallopian, or primary peritoneal cancer: a Korean multicenter retrospective cohort study

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ABSTRACT

Objective: To evaluate the effectiveness and safety of the combination of pegylated liposomal doxorubicin with carboplatin (CD) compared with those of carboplatin and paclitaxel (CP) for platinum-sensitive recurrent ovarian, fallopian, or primary peritoneal cancer in a real-world setting in Korea.
Methods: We enrolled relevant patients from 9 institutions. All patients received CD or CP as the second- or third-line chemotherapy in routine clinical practice during 2013–2018. The primary endpoints were progression-free survival (PFS) and toxicity. The secondary endpoint included the objective response rate (ORR).
Results: Overall, 432 patients (224 and 208 in the CD and CP groups, respectively) were included. With a median follow-up of 18.9 months, the median PFS was not different between the groups (12.7 vs. 13.6 months; hazard ratio, 1.161; 95% confidence interval, 0.923–1.460; p=0.202). The ORR was 74.6% and 80.1% in the CD and CP group, respectively (p=0.556). Age and surgery at relapse were independent prognostic factors. More patients in the CD group significantly experienced a grade 3 to 4 hematologic toxicity and hand-foot syndrome (13.8% vs. 6.3%), whereas grade 2 or more alopecia (6.2% vs. 36.1%), peripheral neuropathy (4.4% vs. 11.4%), and allergic/hypersensitivity reaction (0.4% vs. 8.5%) developed more often in the CP group.

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Conclusions: The safety and effectiveness of chemotherapy with CD in a real-world setting were consistent with the results from a randomized controlled study. The different toxicity profiles between the 2 chemotherapy (CD and CP) regimens should be considered in the clinical practice.

Trial Registration: ClinicalTrials.gov Identifier: NCT03562533

Keywords: Ovarian Cancer; Recurrence; Platinum; Prognosis; Chemotherapy

INTRODUCTION

Most patients with advanced epithelial ovarian, fallopian, or primary peritoneal cancer show disease recurrence after a primary standard treatment including maximal cytoreductive surgery and platinum-based chemotherapy. For patients with a platinum-sensitive disease recurrence, chemotherapy including platinum has been re-administered, regardless of the secondary cytoreductive surgery [1,2]. In several previous studies, secondary cytoreductive surgery was achieved in approximately 60%–75% of patients, and had survival benefit in patients with platinum-sensitive recurrent ovarian cancer (ROC) [3]. In addition, targeted drugs such as bevacizumab and chemotherapeutic agents including paclitaxel, gemcitabine, and pegylated liposomal doxorubicin (PLD), are combined with platinum for treating platinum-sensitive recurrent diseases [4-8].

PLD is a liposomal formulation based on doxorubicin, which is characterized by an extended circulation and an increased tumor uptake and pharmacokinetics. PLD shows mucocutaneous toxicity such as palmar-plantar erythrodysesthesia and myelosuppression as the main toxicity, whereas it is related with a decreased risk of cardiotoxicity and alopecia compared to doxorubicin (<7%) [9,10]. Based on the results of phase II or III study of the PLD [11-14], Caelyx in Platinum Sensitive Ovarian patients (CALYPSO) trial, a phase III study of PLD, has been conducted to compare the efficacy and safety between PLD plus carboplatin (CD) and paclitaxel plus carboplatin (CP) for platinum-sensitive ROC [6]. As a result, the CD group showed an improved progression-free survival (PFS) without the benefit of overall survival. These survival benefits were further enhanced in the subsequent subgroup analyses of patients with certain characteristics, including partial platinum sensitivity or germline *BRCA* mutations [15-17]. In terms of toxicity, it showed lower risks of carboplatin hypersensitivity, peripheral neuropathy, neutropenia, and alopecia while mucositis, nausea and palmar-plantar erythrodysesthesia were observed more frequently in the CD group, but for a short acceptable time. These finding suggest that CD is superior to CP as a second-line chemotherapy with an acceptable toxicity, especially in patient with certain characteristics.

Randomized control trials (RCTs) like CALYPSO trial, performed under idealized conditions, provided the most reliable evidence of the efficacy and toxicity of novel treatment. However, in real clinical situations, there are several considerations including epidemiology, cost of treatments, and patients' heterogeneity, and accordingly, decision making in clinical situation is a highly integrative process of comprehending the evidence of RCTs and the actual clinical situation [18]. For instance, there is a possibility that ethnic differences may make the efficacy and toxicity of CD different because previous studies reported that East Asian population showed different efficacy and toxicity of anti-cancer drug compared with non-Asian population [19]. Therefore, "real-world data" analysis which reflects the actual

clinical situation is needed. Thus, we designed a multi-center retrospective study in a real-world setting to analyze the effectiveness and safety of CD and CP for patients with platinum-sensitive ROC in Korean population [18].

MATERIALS AND METHODS

1. Patients

We conducted this multi-center, retrospective study after obtaining ethical approval and waiver of informed consent from the Institutional Review Boards from the following institutions: Seoul National University Hospital, Sungkyunkwan University School of Medicine, National Cancer Center, Catholic University of Korea Seoul St. Mary's Hospital, University of Ulsan College of Medicine, Yonsei University College of Medicine, Ajou University School of Medicine, Chung-Ang University College of Medicine, Konkuk University School of Medicine. Eligibility criteria were as follows to collect a patient population similar to that registered with CALYPSO: epithelial ovarian, fallopian, or primary peritoneal cancer; platinum-sensitive recurrence; taxane- and platinum-based chemotherapy as the first-line treatment; CD or CP selected by physicians' choice as the second- or third-line therapy from August 2014 to December 2017; and no history of bevacizumab combination with CD or with CP as the second- or third-line therapy.

2. Data collection

We collected clinical information including age at diagnosis, primary site of disease, histology, grade, germline *BRCA1/2* gene mutation, serum CA-125 level, International Federation of Gynecology and Obstetrics (FIGO) stage, tumor size, presence of ascites, and tumor response. Additionally, treatment information, including doses of drugs, cycles, and types of chemotherapy and secondary cytoreductive surgery, was collected. PFS as the primary endpoint was defined as the time interval between the chemotherapy initiation date and the date when disease progression was detected or death. The secondary endpoint included the objective response rate (ORR), safety, tolerability, and duration of chemotherapy. The ORR was defined as the percentage of patients with a complete or partial response among all patients treated with CD or CP, which was determined based on imaging findings according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 for measurable disease [20]. In the case of a non-measurable disease, serum CA-125 levels were utilized based on the Gynecologic Cancer InterGroup criteria [21]. All patients were monitored for disease recurrence until September 2018, according to the clinical policies of each participating institution. In most patients, the tumor markers were examined every cycle, and disease status was assessed every 3 cycles using imaging modality during chemotherapy. After chemotherapy, patients were follow-up every 2–4 months for 2 years then every 3–6 months for the next 3 years with physical examination and tumor markers according to the Korean Society of Gynecologic Oncology guidelines [2]. Imaging modalities such as computed tomography scans were performed every 3 to 12 months, and additional imaging was also performed at the clinicians' discretion if the disease progression was suspected, such as tumor marker elevation. In addition, for each chemotherapy cycle, adverse events between the initial dose and 4 weeks after the last dose in this study were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0 [22].

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3. Statistical methods

Dichotomous variables were analyzed by χ^2 or Fisher's exact test, while continuous variables were compared using Student's t-test or Mann-Whitney U test. Survival was assessed using the Kaplan-Meier method, and the log-rank test was applied to compare the PFS between the 2 groups. Additionally, the Cox proportional hazards model was used to estimate the treatment effect. We used SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA) for analysis, and a p-value <0.05 was considered statistically significant.

RESULTS

1. Patients

From August 2014 to December 2017, a total of 432 patients were enrolled, 224 assigned to the CD group and 208 to the CP group. The data cutoff for this final analysis was in September 2018; the median duration of follow-up was 18.9 months (range, 1–52.7 months). Baseline characteristics are summarized in **Table 1**. In the CD group, there were more patients with disease in an initial FIGO stage III/IV (88.4% vs. 78.8%, p=0.007), but lesser patients with a *BRCA* mutation (15.6% vs. 18.3%, p=0.001), surgery at relapse (22.4% vs. 37.5%, p=0.001), and platinum-free intervals >12 months (44.2% vs. 76.4%, p<0.001) than those in the CP group.

2. Treatment

The most common initial dose of PLD was of 30 mg/m^2, administered in 59.3% (133/224) patients of the CD group (**Table 2**). The median number of chemotherapy cycles was 6 in both treatment groups (range, 1–15 CD; range, 1–15 CP). The proportion of patients who completed at least 6 cycles of therapy was similar in the CD and CP groups (80.4% [180/224] vs. 82.7% [172/208]; p=0.532). The proportion of therapy dose reduction did not differ between the CD and the CP groups (22.3% [50/224] vs. 17.6% [31/176]; p=0.245). Few cycles in both groups were delayed for longer than 7 days due to adverse effect (11.1% for CD vs. 8% for CP; p=0.216). The median treatment duration was longer in the CD group compared with the CP group (21.3 vs. 16 weeks; p<0.001).

3. Efficacy

During the study period, 242 PFS events occurred. The median PFS did not significantly differ between the CD and CP groups (12.7 months vs. 13.6 months; hazard ratio [HR], 1.161; 95% confidence interval [CI], 0.923–1.460; p=0.202) (**Fig. 1**). We sub-analyzed the PFS between the CD and CP groups according to the time interval since the last chemotherapy session (6–12 months vs. >12 months) (**Fig. 2**) and germline *BRCA* status (wild-type vs. mutated) (**Supplementary Fig. 1**) based on the previous researches [15-17]. For patients (n=174) who experienced disease progression at 6–12 months after previous platinum-based chemotherapy, no difference was found between the 2 groups (HR, 0.936; 95% CI, 0.638–1.375; p=0.738). For patients (n=258) who had disease progression >12 months after previous platinum-based chemotherapy, no variation was found between the groups (HR, 1.080; 95% CI, 0.790–1.477; p=0.630). Additionally, there were no statistically significant differences between the 2 groups in germline *BRCA* mutated (HR, 0.930; 95% CI, 0.526–1.643; p=0.802) or *BRCA* wild- type (HR, 1.134; 95% CI, 0.744–1.729; p=0.558) subgroup analysis. Furthermore, the response was evaluable by RECIST in 376 patients. The ORR was of 74.6% and 80.1% in the CD group and the CP group, respectively (p=0.556) (**Supplementary Table 1**).

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Table 1. Baseline characteristics

Variables	Total (n=432)	Carboplatin and PLD (n=224)	Carboplatin and paclitaxel (n=208)	p-value
Age (yr)	54.4±10.6	55.2±10.3	53.5±10.9	0.087*
Primary site of disease				
Ovary	404 (93.7)	208 (93.3)	196 (94.2)	0.889†
Tube	12 (2.8)	7 (3.1)	5 (2.4)	-
Peritoneum	15 (3.5)	8 (3.6)	7 (3.4)	-
Histologic type				
Serous	370 (86.7)	189 (85.1)	181 (88.3)	0.790†
Mucinous	8 (1.9)	4 (1.8)	4 (2.0)	-
Endometrioid	15 (3.5)	8 (3.6)	7 (3.4)	-
Clear cell	19 (4.4)	11 (5.0)	8 (3.9)	-
Histologic grade				
1	29 (7.0)	11 (5.1)	18 (9.2)	0.093†
2	95 (23.0)	59 (27.2)	36 (18.4)	-
3	278 (67.3)	142 (65.4)	136 (69.4)	-
BRCA mutation				
Yes	73 (16.9)	35 (15.6)	38 (18.3)	0.001†
No	144 (33.3)	93 (41.5)	51 (24.5)	-
N/A	215 (49.8)	96 (42.9)	119 (57.1)	-
FIGO stage				
I/II	70 (16.2)	26 (11.6)	44 (21.2)	0.007†
III/IV	362 (83.8)	198 (88.4)	164 (78.8)	-
Measurable disease				
Yes	294 (68.4)	153 (68.3)	141 (68.4)	0.975†
Tumor size				
<5 cm	399 (92.4)	206 (92.0)	193 (92.8)	0.958†
≥5 cm	33 (7.6)	18 (8.0)	15 (7.2)	-
Ascites				
Yes	88 (21.3)	50 (22.9)	38 (19.4)	0.378†
No. of previous lines of chemotherapy				-
One	429 (99.3)	223 (99.6)	206 (99.0)	
Carboplatin	429 (99.3)	223 (99.6)	206 (99.0)	
Taxane	429 (99.3)	223 (99.6)	206 (99.0)	
Two	3 (0.7%)	1 (0.4)	2 (1.0)	
Interval since last chemotherapy (mo)				
Median	14.0 (6–169.1)	10.9 (6–113)	17.0 (6–169.1)	<0.001‡
6–12	174 (40.3)	125 (55.8)	49 (23.6)	<0.001†
>12	258 (59.7)	99 (44.2)	159 (76.4)	-
Surgery for this relapse				
Yes	128 (29.7)	50 (22.4)	78 (37.5)	0.001†

Data are shown as mean±standard deviation or number (%).
FIGO, International Federation of Gynecology and Obstetrics; PLD, pegylated liposomal doxorubicin.
*Student's t-test; †Pearson's χ^2 test; ‡Mann-Whitney U test.

Exploratory analyses examining the impact on PFS of age, interval since last chemotherapy, surgery at relapse, tumor measurability status, size of tumor, histology, grade, CA-125 level at recurrence, germline *BRCA* mutation status, and treatment group were performed using Cox proportional hazards regression. Age and surgery at relapse maintained a significance in the multivariate Cox regression model (**Table 3**). After adjusting by age, interval since last chemotherapy, surgery at relapse, measurability status of tumor, germline *BRCA* mutation status, and CA-125 level at recurrence, there was no statistically significant difference between the CD and CP group (HR, 0.862; 95% CI, 0.664–1.120; p=0.267).

4. Toxicity

A total of 400 patients were included in the safety analysis, and the detailed toxicity profile was analyzed per patients (**Table 4**). Overall, more patients in the CD group significantly experienced a grade 3 to 4 hematologic toxicity compared with the CP group (grade 3 to

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Table 2. Treatment administration

Variables	Carboplatin and PLD (n=224)	Carboplatin and paclitaxel (n=208)	p-value
Initial dose of PLD			-
30 mg/m²	133 (59.3)	-	
40 mg/m²	65 (29.0)	-	
50 mg/m²	26 (11.6)	-	
Initial dose of paclitaxel			-
175 mg/m²	-	197 (94.7)	
135 mg/m²	-	11 (5.3)	
Initial dose of carboplatin			-
AUC 6	0	3 (1.7)	
AUC 5	219 (97)	204 (97.8)	
AUC 4	2 (1.8)	1 (0.6)	
AUC 3	3 (1.2)	0	
No, of chemotherapy cycles	6 (1–15)	6 (1–15)	0.723†
Completed at least 6 cycles	180 (80.4)	172 (82.7)	0.532*
Cumulative cycles of chemotherapy	1,393	1,271	0.671†
Duration of chemotherapy (wk)	21.3 (1–89.1)	16 (1–98)	<0.001†
Dose reduction	50/224 (22.3)	31/176 (17.6)	0.245*
Delay of modification for AEs	154/1,393 (11.1)	84/1,050 (8)	0.216†

Values are presented as median (interquartile range) or number (%).
AE, adverse effect; AUC, area under the curve; PLD, pegylated liposomal doxorubicin.
*Pearson's χ^2 test; †Mann-Whitney U test.

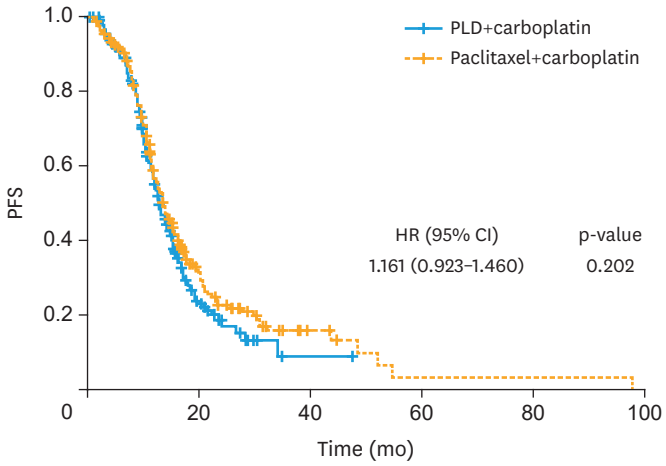

Fig. 1. PFS according to the chemotherapy regimens.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin.

4 neutropenia 27.7% vs. 8.0%; p<0.001, grade 3 to 4 thrombocytopenia 13.8% vs. 2.3%; p<0.001, grade 3 to 4 anemia 16.5% vs. 1.7%; p<0.001). Grade ≥2 alopecia (6.2% vs. 36.1%; p<0.001), peripheral neuropathy (4.4% vs. 11.4%; p=0.008), and allergic/hypersensitivity reaction (0.4% vs. 8.5%; p<0.001) occurred more often in the CP group. Otherwise, Hand-foot syndrome (13.8% vs. 6.3%; p=0.009) and mucositis (8.5% vs. 0%; p<0.001) occurred more in the CD group. In addition, we also conducted safety analyses according to the initial dose of CD regimens to identify the difference of toxicity compared to the CALYPSO trial. Grade 3 to 4 hematologic toxicity and grade 2≥ hand-foot syndrome increased gradually as PLD dose increased, but the overall toxicity profile of each regimen were consistently observed in the subgroup analysis as described above (**Supplementary Tables 2-4**).

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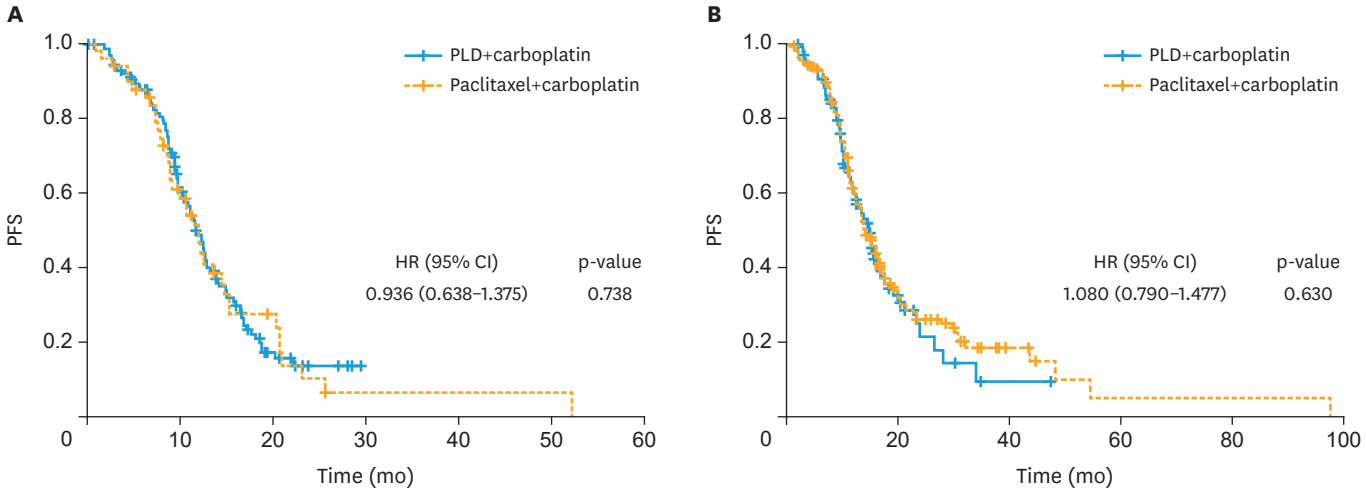

Fig. 2. PFS between the CD and CP groups according to the interval since the last chemotherapy session (A) 6–12 months (B) >12 months.
CD, pegylated liposomal doxorubicin with carboplatin; CI, confidence interval; CP, carboplatin and paclitaxel; HR, hazard ratio; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin.

Table 3. Multivariate analysis of the predictive factors of progression free survival

Variables	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at initial diagnosis (yr)	1.018 (1.007–1.029)	0.001	1.014 (1.002–1.027)	0.021
Histologic type				
Serous	1	0.449	-	-
Mucinous	2.029 (0.901–4.569)	-	-	-
Endometrioid	0.859 (0.442–1.670)	-	-	-
Clear cell	1.207 (0.660–2.207)	-	-	-
Histologic grade				
1	1	0.290	-	-
2	1.545 (0.897–2.662)	-	-	-
3	1.584 (0.950–2.641)	-	-	-
BRCA mutation				
Yes	0.849 (0.602–1.197)	0.350	1.137 (0.950–1.359)	0.160
FIGO stage				
I/II	1	-	-	-
III/IV	1.224 (0.885–1.694)	0.222	-	-
Measurable disease				
Yes	1.406 (1.110–1.781)	0.005	1.128 (0.873–1.458)	0.355
Tumor size				
<5 cm	1	-	-	-
≥5 cm	1.296 (0.822–2.044	0.264	-	-
Ascites				
Yes	1.353 (0.997–1.836)	0.052	1.269 (0.973–1.650)	0.109
CA125>100U/mL				
Yes	1.431 (1.134–1.806)	0.003	1.267 (0.973–1.650)	0.079
Interval since last chemotherapy (mo)				
6–12	1	-	1	-
>12	0.674 (0.534–0.849)	0.001	0.826 (0.633–1.078)	0.160
Surgery for this relapse			1	
Yes	0.487 (0.373–0.636)	<0.001	0.566 (0.419–0.764)	<0.001
Treatment arm				
Carboplatin and paclitaxel	1	-	1	-
Carboplatin and PLD	1.161(0.923–1.460)	0.202	0.862 (0.664–1.120)	0.267

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; PLD, pegylated liposomal doxorubicin.

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Table 4. Adverse events according to treatment allocation

Adverse event	Carboplatin and PLD (n=224)			Carboplatin and paclitaxel (n=176)			p-value
	Any grade	Grade ≥2	Grade 3–4	Any grade	Grade ≥2	Grade 3–4	
Neutropenia	152 (67.9)	-	62 (27.7)	67 (38.1)	-	14 (8.0)	<0.001‡,‖
Thrombocytopenia	68 (30.4)	-	31 (13.8)	32 (18.2)	-	4 (2.3)	<0.001‡,‖
Anemia	169 (75.4)	-	37 (16.5)	119 (67.6)	-	3 (1.7)	<0.001‡,‖
Alopecia	34 (34.1)*	6 (6.2)*	-	98 (90.7)†	39 (36.1)†	-	<0.001‡,¶
Nausea/vomiting	25 (11.2)	15 (6.7)	-	26 (14.8)	12 (6.8)	-	0.962‡,¶
Constipation/diarrhea	17 (7.6)	8 (3.5)	-	21 (11.9)	6 (3.4)	-	0.930‡,¶
Fatigue	8 (3.6)	6 (2.7)	-	8 (5.2)	2 (1.2)	-	0.475§,¶
Mucositis	30 (13.4)	19 (8.5)	-	2 (1.1)	0	-	<0.001‡,¶
Neuropathy	21 (9.4)	10 (4.4)	-	35 (19.9)	20 (11.4)	-	0.008‡,¶
Cardiovascular	9 (4.0)	4 (1.8)	-	4 (2.3)	3 (1.7)	-	0.951‡,¶
Allergic reaction	4 (1.7)	1 (0.4)	-	25 (14.2)	15 (8.5)	-	<0.001‡,¶
Hand-foot syndrome	31 (13.8)	21 (9.4)	-	11 (6.3)	5 (2.8)	-	0.009‡,¶
Arthralgia/myalgia	16 (7.1)	5 (2.2)	-	11 (6.3)	8 (4.6)	-	0.236§,¶

PLD, pegylated liposomal doxorubicin
*Evaluable in 97 patients; †Evaluable in 108 patients; ‡Pearson's χ^2 test; §Fisher's exact test; ‖Grade 3–4; ¶Grade ≥2.

DISCUSSION

In order to improve patient tolerance and survival outcomes in ROC, secondary cytoreductive surgery for selected patients, other carboplatin-based combination chemotherapies, such as gemcitabine, topotecan, and PLD, and the addition of target therapeutic agents have been investigated in numerous randomized clinical trials [6-8,23-27]. In this report, a multicenter, observational retrospective cohort study was conducted in a real-world clinical setting to assess the effectiveness and safety of a CD regimen based on the CALYPSO trial [6,18]. It showed that the effectiveness and safety profile of a CD regimen are generally consistent with the CALYPSO trial, and demonstrate that the CD regimen is effective as a second-line drug of chemotherapy in the platinum-sensitive ROC.

Doxorubicin was used primarily in the treatment of ROC, which inhibits the enzymatic activity of topoisomerase II, and leads to double-stranded DNA breaks through several other mechanisms [27]. However, its use has been reduced due to the emergence of other chemotherapeutic agents such as paclitaxel, gemcitabine, and topotecan, and the serious adverse effects like cardiotoxicity [28]. Therefore, PLD was designed to have a similar efficacy, and fewer side effects compared to conventional doxorubicin. It is a unique formulation of conventional doxorubicin in which surrounded with a bilayer of liposome, that is encapsulated by a polyethylene glycol (PEG) layer. This PEG coat interferes with molecular breakdown and drug release. Furthermore, the size of the liposomes is approximately 100 nm, which prevents them from entering tissues with tight capillary junctions, and selectively deposits the PLD into the tumor. These molecular characteristics prolong the plasma half-life and increase the drug concentration in the tumor [28,29]. With these merits, PLD has been incorporated into the standard treatment of ROC on the basis of the several clinical trials.

In this study, the median PFS of the CD group was comparable to that of the CALYPSO trial (12.7 months vs. 11.3 months) [6]. However, unlike the CALYPSO trial, the median PFS of the CD group did not statistically improve compared to the median PFS of the CP group (HR, 1.161; CI, 0.923–1.460; p=0.202; 12.7 months vs. 13.6 months) (**Fig. 1**). These results were similarly observed in the subgroup analysis performed according to time intervals since the last chemotherapy (6–12 months vs. >12 months) (**Fig. 2**). These differences between the

CALYPSO trial and our study can be explained by the high prevalence of patients with worse prognostic factors in the CD group of our study; there were more patients presenting an initial advanced stage, germline *BRCA* wild-type, no surgery at relapse, and platinum-free intervals 6–12 months. The exact reason for this discrepancy between a real-world research and a randomized trial is unknown. One possible explanation is that in previous study the CD regimen had a more favorable risk-benefit profile than CP in patients with partially platinum-sensitive ROC [17]. Consequently, this result was reflected in the actual clinical circumstance, and the CD regimen has been prescribed preferentially for partially-sensitive ROC in this study. In addition, we performed subgroup survival analysis according to the germline *BRCA* status (wild-type vs. mutated), based on the findings which is PLD caused double-stranded DNA breaks and improved survival outcome of *BRCA* mutated patients. However, unlike previous reports, no significant survival differences were observed between the groups (**Supplementary Fig. 1**).

In the treatment information analysis, the median number of chemotherapy cycles was 6 in both treatment cohorts. However, the completion rate at 6 cycles was lower in the CD group than in the CP group, although it was not statistically significant (80.4% vs. 82.7%, p=0.532). Moreover, this rate was even lower than in the CALYPSO trial (85.0% for CD group). These differences may be due to physicians chose their preferred PLD dosage for each patient, and 91 patients (40.6%) received higher PLD dosage than CALYPSO trial. In a detailed assessment of the overall adverse effects, the incidence of all adverse effects in our retrospective study was lower than in the CALYPSO trial. In general, the efficacy and toxicity was higher in east Asian population than in Caucasian [19]. These differences because adverse events are generally reported more rigorously in clinical trials than in retrospective studies [18]. Grade ≥2 sensory neuropathy (4.4% vs. 11.4%, p=0.008), allergic/hypersensitivity reactions (0.4% vs. 8.5%, p<0.001) and alopecia (6.2% vs. 36.1%, p<0.001) occurred more frequently in the CP group than in the CD group. On the contrary, grade ≥2 mucositis (8.5 vs. 0%, p<0.001) and hand-foot syndrome (9.4% vs. 2.8%, p=0.009), particular side effects of the CD regimen, appeared more in the CD group than in the CP group. No patients developed cardiotoxicity in either cohort. These results were consistent with the CALYPSO trial. Regarding hematologic toxicities, grade 3 to 4 neutropenia, thrombocytopenia, and anemia were significantly more frequent in the CD group compared to the CP group although neutropenia was more frequently reported in the CP group in the CALYPSO trials [6,17]. These discrepancies between the CALYPSO trial and our study may be due to the difference of PLD dosage between our retrospective study and clinical trial. Accordingly, the subgroup safety analysis conducted based on the PLD dosage. Grade 3 to 4 hematologic toxicity was still higher in the CD group than in the CP group, but neutropenia and thrombocytopenia in the 30mg/m^2 PLD group were even lower than in the CALYPSO trial. This significant difference between real-world and clinical trial may be due to the prevalence of patients who underwent 2 lines of previous chemotherapy. Only 3 (0.7%) patients had received 2 lines of chemotherapy before our study, whereas 146 (14.9%) patients had previously received 2 lines of chemotherapy before in the CALYPSO trial. Because patients become more vulnerable with more chemotherapy, the discrepancy in the toxicity analysis between the CALYPSO trial and our study may be explained [5,30]. In conclusion, we suggest that CD regimen with 30 mg/m^2 PLD can be used as a second line chemotherapy for patients with chemotherapy-induced neuropathy or history of severe hematologic toxicity.

This study presents some limitations, such as the possible occurrence of a selection bias caused by those inherent in the design of a retrospective observational study. Because

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different physicians chose the chemotherapy regimen and dosage at the physicians' discretion for each patient, the baseline characteristics of patients in both CD and CP groups were not consistent with CALYPSO trial. In addition, tumor response with toxicity was evaluated retrospectively; the safety and effectiveness of our results should be interpreted cautiously considering heterogeneous therapeutic and follow up strategies. Moreover, while the combination therapy with bevacizumab has been shown to be more effective in treating with a platinum-based combination therapy for ROC patients, only a small phase II clinical trial was performed for the combination of the CD regimen with bevacizumab [23]. In this study, there were no data considering the combination of bevacizumab in the CD regimen. Additionally, although the combination of the CP regimen with bevacizumab (CPB) has been used in first-line therapy in the treatment of ROC [8], there were no data comparing the efficacy and safety of the CD regimen with the CPB regimen in our research. Therefore, further research is needed to find the answers to these questions.

In conclusion, to our knowledge, our retrospective observational study is a relatively large study that evaluated the effectiveness and safety of the CD regimen in a real-world setting. With the results of previous RCTs, the combination of carboplatin and PLD has emerged as an attractive alternative in the treatment of platinum-sensitive ROC [6,17,26]. In this study, we demonstrated that the CD regimen offers an analogous effectiveness and safety profile in a real-world setting compared to previous clinical trials with platinum-sensitive ROC. Therefore, when treating patients with platinum-sensitive ROC, CD regimen could be considered as one of the second-line treatment options.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Response by Response Evaluation Criteria In Solid Tumors according to the treatments (evaluable in 376 patients)

Click here to view

Supplementary Table 2

Subgroup analysis of adverse events according to initial PLD dosage (30 mg/m^2) between the CD and CP groups

Click here to view

Supplementary Table 3

Subgroup analysis of adverse events according to initial PLD dosage (40 mg/m^2) between the CD and CP groups

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Supplementary Table 4

Subgroup analysis of adverse events according to initial PLD dosage (50 mg/m^2) between the CD and CP groups

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Supplementary Fig. 1

PFS between the CD and CP groups according to the germline *BRCA* status (A) germline *BRCA* wild-type (B) germline *BRCA* mutation (+)

Click here to view

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