

Retrospective Analysis Of Comparative Outcomes In Recurrent Platinum-Sensitive Ovarian Cancer Treated With Pegylated Liposomal Doxorubicin (Lipo-Dox) And Carboplatin Versus Paclitaxel And Carboplatin

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Chia-Sui Weng ^{1,*}
Chao-Chih Wu ^{2,*}
Tze-Chien Chen ¹
Jen-Ruei Chen ¹
Chueh-Yi Huang ¹
Chih-Long Chang ¹⁻³

¹Department of Obstetrics and Gynecology, MacKay Memorial Hospital, Taipei, Taiwan; ²Department of Medical Research, MacKay Memorial Hospital, New Taipei City, Taiwan; ³Department of Medicine, Mackay Medical College, New Taipei City, Taiwan

*These authors contributed equally to this work

Purpose: The aim of this study is to analyze the outcomes of platinum-sensitive (PS) recurrent ovarian cancer treated with pegylated liposomal doxorubicin and carboplatin (CD) versus paclitaxel and carboplatin (CP). Clinical features were examined to characterize the patient population that would benefit from CD.

Materials and methods: This is a retrospective review of 122 cases at a tertiary hospital. Patients with PS recurrent ovarian cancer who received CD or CP were included. Progression-free survival (PFS) and overall survival (OS) were evaluated through the Kaplan–Meier method and log-rank test. Cox proportional hazards regression was used to examine PFS predictors.

Results: In total, 122 patients (75% with first recurrence and 25% with second recurrence) were included. The majority of the patients were diagnosed at an advanced stage and with the histology of serous carcinoma. Median PFS and OS were 14.8 and 55.5 months in the CD group and 13.5 and 56.8 months in the CP group. Subgroup analysis of patients revealed that the CD group had longer median PFS than the CP group among patients with PFI>12 months. Additionally, during the second recurrence, longer PFS was observed in the CD group than in the CP group (medians 22.3 and 13.5 months, respectively, $p = 0.019$).

Conclusion: Comparable outcomes in recurrent platinum-sensitive ovarian cancer treated with CD versus CP were presented in this study. Longer PFS in CD group was observed among patients with PFI for more than 12 months or in second recurrence.

Keywords: Lipo-Dox, platinum-sensitive ovarian cancer

Introduction

Ovarian cancer is an intractable disease with repeated recurrences and has the worst prognosis among all gynecologic cancers.¹ More than 238,000 new cases are diagnosed worldwide each year.² Although most patients with advanced cancer have responded well to initial cytoreductive surgery followed by chemotherapy, recurrence of the disease is frequent.^{3,4} Patients commonly experience four to five cycles of chemotherapy and determining the drugs for recurrent ovarian cancer is perplexing. Tumor histology, line of therapy, and quality of life due to the adverse effects of treatment should all be considered.

Correspondence: Chih-Long Chang
Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan
Tel +886-2-25433535
Fax +886-2-25232448
Email clchang@mmc.edu.tw

For decades, taxane with platinum-based treatment has played a major role in platinum-sensitive (PS) recurrent ovarian cancer. However, hair loss and neuropathy caused by the treatment significantly decrease patients' quality of life.⁵ Therefore, several carboplatin-based combinations had been explored.^{6–8} In 2010, the Calypso trial demonstrated that pegylated liposomal doxorubicin with carboplatin (CD) showed superiority over paclitaxel and carboplatin (CP) in progression-free survival (PFS) and less overall toxicity.^{9,10} CD regimen soon became an attractive alternative for ovarian cancer treatment.

Pegylated liposomal doxorubicin (PLD) is one of the first nanotechnology-based anti-cancer drugs with reduced side effects.^{11–13} Doxorubicin molecules were loaded in liposome vesicles and have been established as an active cytotoxic agent for recurrent ovarian cancer.^{7,8} Liposomes are composed of phospholipids and cholesterol on the lipid bilayer and are coated with polyethylene glycol.^{14,15} Unique pharmacokinetic and pharmacodynamic properties are observed from the different phospholipid formulations. Lipo-Dox[®] (TTY) is formulated with distearoylphosphatidylcholine (DPLD), while hydrogenated soy phosphatidylcholine (HPLD) is used in Doxil[®] (Janssen). Compared with Doxil, Lipo-Dox demonstrated a lower clearance rate, longer half-life, and smaller distribution volume, indicating its higher stability in plasma.¹⁶

In the Calypso trial, HPLD was used while in our institute, DPLD was administered in CD regimen. Therefore, a confirmatory study to the Calypso trial was prompted. This study is aimed to present the outcomes of PS recurrent ovarian cancer treated with CD using DPLD versus CP. Factors influencing the efficacy of each regimen were analyzed.

Materials And Methods

Study Population

This is a retrospective single institutional study. The medical records of patients with PS recurrent epithelial ovarian cancer, fallopian tube cancer, or peritoneal cancer from 2009 to 2016 were collected. The study was conducted in accordance with the ethical standards of Declaration of Helsinki and was approved by the institutional review board of MacKay Memorial Hospital. A waiver of patient consent was granted because the research involved no more than minimal risk to the participants and the waiver will not adversely affect the rights and welfare of the participants. Patients were considered eligible if

recurrence occurred more than 6 months from previous platinum-based treatment and received CD or CP during the relapse.

Study Design

The regimen for CD was DPLD (30 mg/m², Lipo-Dox[®], TTY Biopharm Co., Ltd, Taipei, Taiwan) plus carboplatin (AUC5) every 4 weeks and CP was paclitaxel (175 mg/m², Taxol[®]; Bristol-Myers Squibb) plus carboplatin (AUC5) every 3 weeks. Cytoreductive surgery with residual tumor of <1 cm was considered an optimal cytoreductive surgery. Tumor response was evaluated for at least 4 weeks after treatment according to RECIST and GCIG CA-125 criteria. Disappearance of all tumor lesions, according to both computed images and CA-125 level, was considered a complete response. A reduction in CA-125 level $\geq 50\%$ or measurable lesions was defined as a partial response. Progressive disease was defined as new lesion development, an increase in CA-125 level $>25\%$ or increase of initial measurable lesions. Stable disease was defined as a condition not meeting any of the aforementioned criteria. The main outcome was PFS which was determined from the date of first chemotherapy to the date of disease progression, death, or final follow-up. Overall survival (OS) was measured from the date of first chemotherapy to the date of death or final follow-up.

Statistical Analysis

Patient demographics and clinical characteristics were compared using χ^2 test and Wilcoxon rank-sum test. PFS and OS were evaluated through the Kaplan–Meier method and log-rank test. Multivariate analysis of predictive factors was performed with significant variables ($p < 0.1$) in the univariate analysis, and hazard ratios (HR) with 95% CI were calculated. All statistical analyses were performed using Statistical Package for Science Software (IBM SPSS, version 20.0, Armonk, NY, USA), and a p -value < 0.05 was considered statistically significant.

Results

In total, 122 patients with recurrent PS ovarian cancer who received CD or CP chemotherapy in our hospital were included. Demographic and clinical characteristics of these patients are shown in Table 1. The mean ages of the patients were 56 and 53 years, respectively. In both groups, approximately 75% were in first recurrence and 25% with two recurrences. The majority of the patients were diagnosed at an advanced stage (stage III

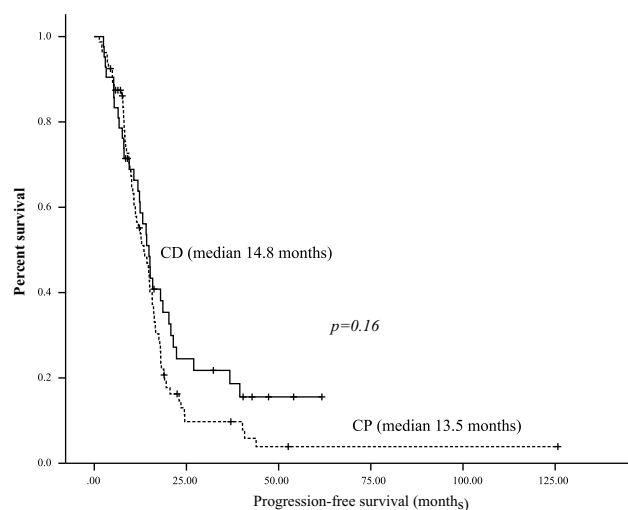
Table I Patient Demographics (N = 122)

Patient Characteristics					
	CD		CP		P
	N	%	n	%	
Total	42		80		
Age					0.1149
Mean	56		53		
Range	31–72		33–74		
Status					0.7661
1st recurrence	31	74	61	76	
2nd recurrence	11	26	19	24	
Initial FIGO Stage					0.0495
I-II	8	19	29	36	
III-IV	34	81	51	64	
Primary Histology					0.3376
Serous	34	80	54	68	
Endometrioid	2	5	13	16	
Clear cell	4	10	9	11	
Mucinous	2	5	3	4	
Other	0	0	1	1	
Platinum Free Interval					0.7668
Median	12.4		14		
Range	6.2–79.6		6.2–76.1		
6–12 months	19	45	30	38	
>12 months	23	55	50	62	
No. Of Chemotherapy Courses					0.426
3	5	12	4	5	
4	1	2	3	4	
5	1	2	5	6	
≥6	35	84	68	85	
Surgery For This Recurrence					0.3787
No surgery	21	50	31	39	
Optimal cytoreductive surgery	19	45	41	51	
Suboptimal cytoreductive surgery	2	5	8	10	
Chemotherapy Response					0.1359
Complete response	18	43	51	64	
Partial response	7	17	10	12	
Stable disease	8	19	11	14	
Progressive disease	9	21	8	10	

or IV, 81% in the CD group and 64% in the CP group) with histologically confirmed serous carcinoma (80% in the CD group and 68% in the CP group). Patients with an initial stage higher than IC were treated with CP as

adjuvant chemotherapy after the primary surgery. The period between the final platinum treatment and relapse ranged from 6.2 to 79.6 months with medians of 12.4 and 14 months, respectively. Similarly, in both groups, the disease recurred within 6 to 12 months in 40% of the patients, 40% of the patients recurred within 12 to 24 months, and 20% of them recurred after 24 months. Detailed toxicities of chemotherapy were not reported in this study; however, the side effects were tolerable and more than 80% of the patients in each group received more than 6 cycles of chemotherapy. Those who received only 3 cycles were mainly by reason of disease progression. Surgical intervention was performed in 50% and 61% of the patients in the CD and CP groups and optimal cytoreductive surgery was achieved in 90% and 83%, respectively. Regarding metastatic sites, relapse with lymph node metastasis was more prevalent in the no surgery group (50% vs 25%).

Evaluation of CA-125 levels and computed tomography indicated response rate and disease control rate of 60%, 79% in CD group and 76%, 90% in CP groups. Median PFS was 14.8 months in the CD group and 13.5 months in the CP group (Figure 1). Median OS was 55.5 months in the CD group and 56.6 months in the CP group. Patients were stratified for subgroup analysis according to platinum-free interval (PFI) and times of recurrence. The results revealed that median PFS was statistically different in the PFI>12 months group. Individuals with PFI>12 months had median PFS as 20.8 and 15.8 months when treated with CD versus CP (Figure 2). In addition, as shown in Figure 3, during the second relapse, longer PFS

**Figure 1** Progression-free survival of CP and CD groups.

was observed in the CD group than in the CP group (medians of 22.3 months and 13.5 months, respectively, $p = 0.02$).

Exploratory analyses were conducted to determine the prognostic factors including age, initial International Federation of Gynecology and Obstetrics stage, histologic subtypes, surgery at relapse, platinum-free interval, chemotherapy for first relapse, chemotherapy for second relapse, and CA-125 level using Cox proportional hazards regression. Age, PFI, chemotherapy for first and second relapse were statistically significant and multivariate analysis was performed. As shown in Table 2, use of CD in

the second relapse was statistically significant (hazard ratio [HR], 0.36; $p = 0.038$).

Discussion

With the biological nature of repeated recurrences, quality of life has become an essential factor in decision-making about ovarian cancer treatment. Despite the effectiveness of paclitaxel in ovarian cancer survival, its major side effects of hair loss and neuropathy are distressing for most patients. The Calypso study provided clear proof of therapeutic advantage of CD using HPLD in PS recurrent ovarian cancer with less toxicity. In this study, real-world

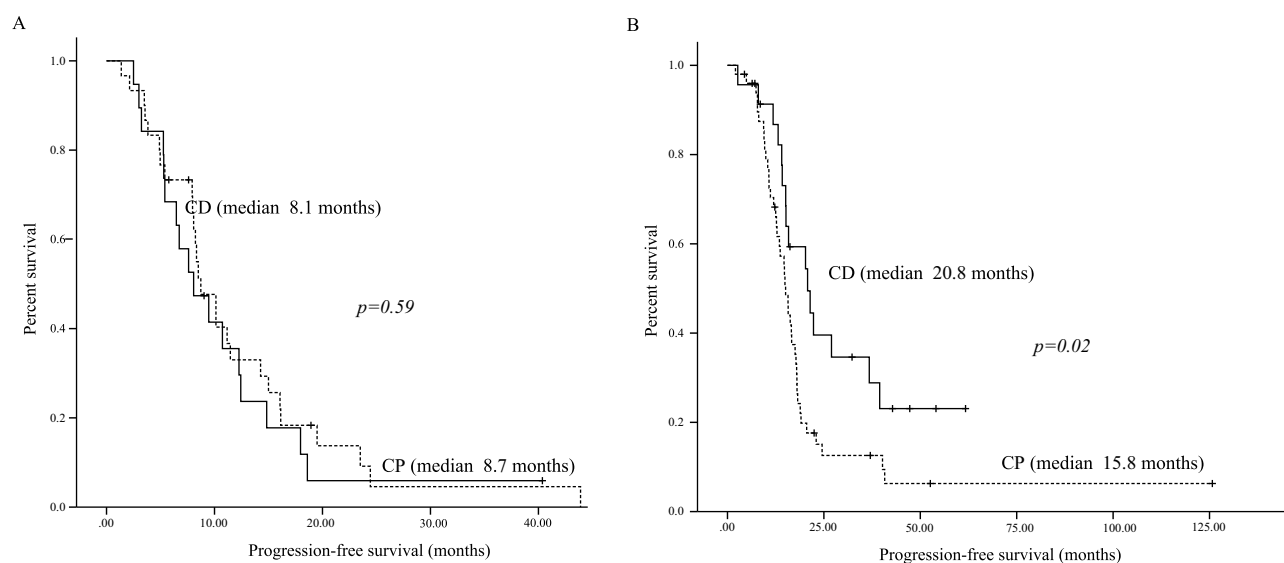


Figure 2 Progression-free survival in relation to platinum-free interval (PFI). (A) Patients with PFI 6–12 months. (B) Patients with PFI >12 months.

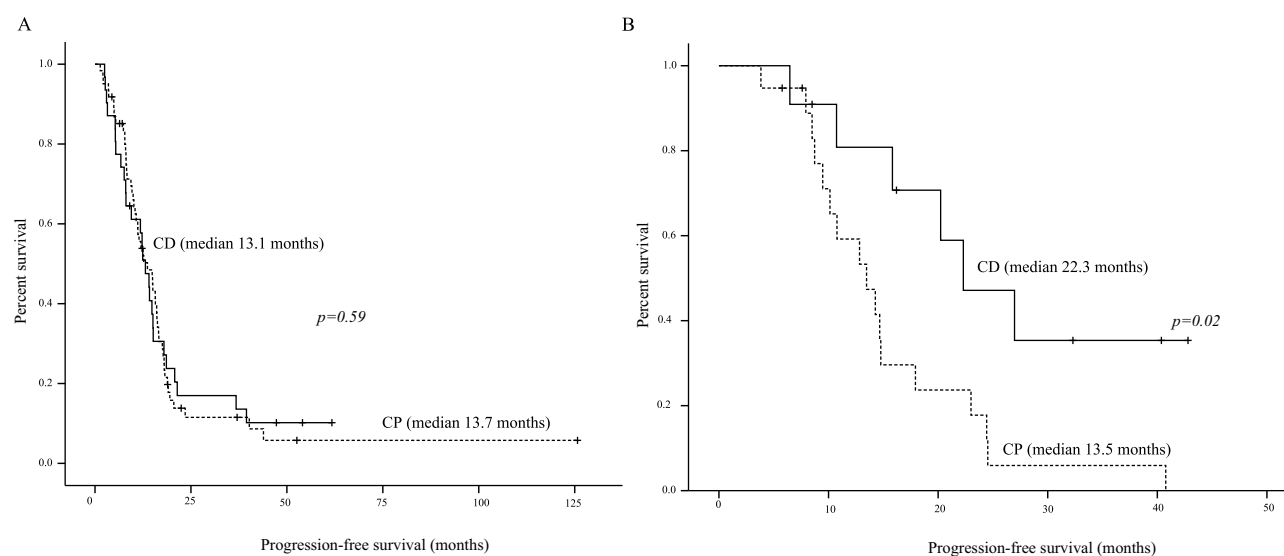


Figure 3 Progression-free survival based on relapse. (A) Patients with first recurrence. (B) Patients with second recurrence.

Table 2 Multivariate Analysis Of Predictive Factors On Progression-Free Survival After Second Relapse

Factors	Multivariate Cox Regression Model		
	HR (95% CI)	95% CI	p-Value
Age			
<50	1	0.09–1.00	0.05
≥50	0.3		
Chemotherapy for First Relapse			
CP	1	0.15–1.81	0.301
CD	0.36		
PFI			
6–12M	1	0.21–1.35	0.186
>12M	0.54		
Chemotherapy for Second Relapse			
CP	1	0.14–0.94	0.038
CD	0.51		

experience of CD using DPLD in PS ovarian cancer is presented.

In our study, the PFS and OS were 14.8 and 55.5 months for CD group which is comparable with the Calypso study when a median of 11.3 and 30.7 months was reported.^{9,17} In comparison to the Calypso study, the patient population reported in this study were younger and more percentage of patients received cytoreductive surgery for the recurrence. Four other separate trials of CD in recurrent PS ovarian cancer had been published showing similar median PFS as 9.4–12 months.^{18–21} In regard to response rate of disease progression, the Calypso study reported 21% and 20% in CD and CP groups whereas in our population, 21% and 10% were observed in CD and CP groups. More cytoreductive surgeries were performed in the present study may contribute to the increased response rate in our CP group.

In this study, median PFS between first and second recurrence was equivalent (12.7 and 12.5 months for first and second recurrence), not shortened as anticipated.²² Notably prolonged PFS for the CD group on second relapse was observed (Figure 3). Multivariate analysis further confirmed that use of CD is a significant predictor on PFS (HR, 0.36; $p = 0.038$). The superiority of CD to CP for PFS was even more evident for individuals with PFI >12 months (Figure 2). In studies of recurrent ovarian cancer, patients with first or second relapses were generally grouped together, and the

response to second- or third-line treatment is poorly described independently. In present study, PFS was superior in CD group than CP group in the second relapse which was not observed in the first relapse. Recent advances in the molecular basis of ovarian cancer cells, including intra-tumoral and inter-tumoral heterogeneity lead us to better understanding of the mechanisms for tumor recurrence and therapeutic resistance.^{23,24} Cancer stem cells with different characteristics may survive from therapies eliminating fast-dividing tumor cells. Growth from the stem cells slowly develops recurrent tumors which may be genetically distinct from previous tumors, thus causing multiple rounds of recurrences and metastases. In summary, alteration of the molecular portraits of tumor cells during the second relapse may contribute to the improved PFS for patients receiving CD.

Over the past decades, much effort has been invested to investigate the molecular basis that predicts the chemosensitivity of recurrent ovarian cancer. Assessment of tumor subtype-specific mutations and molecular aberrations indicated distinct clinical behaviors in recurrent ovarian cancer.²⁵ Most notably, patients with *BRCA* mutations exhibited delayed relapse and improved prognosis, regardless of platinum sensitivity.²⁶ *BRCA*-family genes play crucial roles in homologous recombination in the DNA repair pathway (HRD), which is the common pathway for repairing the double-strand breaks caused by chemotherapy. This subset of ovarian cancer with mutation of *BRCA* or other inherited mutations, such as those of *BARD1*, *CHECK2*, and *PALB2*, related to HRD is referred to as the “BRCAness” phenotype.^{27,28} Hypersensitivity to platinum and a high response rate to PLD were observed among women with *BRCA* mutation.²⁹ Moreover, the clinicopathological features of *BRCA1* and *BRCA2* mutation were discovered to be distinct. *BRCA*-associated ovarian cancer, especially that associated with *BRCA1*, tends to metastasize to visceral organs.³⁰ Furthermore, interesting results emerged when investigators started dissecting the implications of *BRCA1* and *BRCA2* for nonplatinum agents. Both *BRCA1*- and *BRCA2*-associated ovarian cancer have been discovered to be more sensitive to PLD compared with *BRCA* wild type-associated ovarian cancer,^{31,32} whereas *BRCA1*-associated ovarian cancer may be more resistant to taxanes.^{33,34} Determining the chemosensitivity of recurrent ovarian cancer became even more complex after restored protein function was reported after treatment for cancer related to secondary *BRCA* mutation.³⁵ Investigation of this reversion and its clinical correlations are eagerly anticipated.

Latest treatment of ovarian cancer had even gone beyond combination chemotherapy. Breakthrough drugs

as PARP inhibitors,³⁶ anti-angiogenesis bevacizumab³⁷ and immunotherapy³⁸ had yielded promising results. Therefore, current efforts should be focused on optimizing the use of chemotherapy with multiple alternative strategies being carefully evaluated and employed when appropriate in the treatment of ovarian cancer.

The retrospective nature of the study with small sample size is the limitation of our study. Patients were treated with CD or CP according to the physicians' preference which may cause selection bias. Moreover, toxicity profiles were not precisely documented in the medical records and could not be analyzed in our study. Inclusion of consecutive cases from multiple institutes is necessary to confirm our results.

In conclusion, real-world experience of comparable outcomes in recurrent PS ovarian cancer treated with CD using DPLD versus CP was presented in this study. Improved PFS in individuals treated with CD was observed in the subgroup of patients with PFI for more than 12 months or during second recurrence. Future sequential identification of genomic tumor changes must be exploited and may influence choices for chemotherapeutic drugs.

Ethics Approval And Consent To Participate

This study was conducted in accordance with the regulations on patient confidentiality and the ethical standards of Declaration of Helsinki. This research was approved by the institutional review board of MacKay Memorial Hospital. A waiver of patient consent was granted because the research involved no more than minimal risk to the participants and the waiver will not adversely affect the rights and welfare of the participants.

Available Of Data And Materials

Please contact the corresponding author (Dr Chih-Long Chang) for data requests.

Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflict of interest in this work.

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