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GYNECOLOGIC ONCOLOGY

Efficacy of pegylated liposomal doxorubicin maintenance therapy in platinum-sensitive recurrent epithelial ovarian cancer: a retrospective study

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Abstract

Objective To examine the effectiveness of pegylated liposomal doxorubicin (PLD) maintenance therapy (intravenous administration at dose 40 mg/m^2 on day 1, repeated every 4 weeks) after first-line salvage chemotherapy for platinum-sensitive recurrent epithelial ovarian cancer.

Methods This retrospective cohort study examined women with a first recurrence of platinum-sensitive epithelial ovarian cancer diagnosed between 2005 and 2015. Eligible cases had PLD maintenance following the first-line salvage chemotherapy ($n=28$). Outcomes of interest included adverse events related to PLD maintenance therapy and survival outcome after the first recurrence.

Results The median number of PLD maintenance cycles was 7.5 (range 2–26), and 11 (40%) women received ≥ 12 cycles. The median cumulative dose of PLD was 432.5 mg/m^2 (range 120–1200 mg/m^2). No women developed cardiotoxicity or secondary malignancies. There were 16 (57%) women who developed any grade of adverse events, including 3 (11%) women who developed grade 3 adverse events. There were no grade 4 adverse events. The most common adverse event was mucositis ($n=7$, 25%). Dose reduction due to adverse events occurred in 14 (50%) women including 3 (11%) women with discontinuation due to toxicity. Median progression-free survival and overall survival after the initiation of PLD maintenance was 14.5 months (2-year rate 21.1%) and 51.2 months (5-year rate 43.4%), respectively.

Conclusion Our study suggests that PLD maintenance therapy for platinum-sensitive recurrent ovarian cancer is relatively well tolerated with the use of dose reduction to manage toxicity. Our study suggests that PLD maintenance therapy may be effective for women with platinum-sensitive recurrent epithelial ovarian cancer.

Keywords Ovarian neoplasms · Recurrence · Platinum sensitive · Liposomal doxorubicin · Maintenance · Survival

Introduction

Epithelial ovarian cancer represents one of the most frustratingly tenacious disease entities amongst malignancies despite impressive surgical and chemotherapeutic advances over the last several decades. While a large majority of patients achieve a complete response to primary therapy, approximately 75% of women will experience recurrent

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disease, typically within 18 to 28 months following completion of primary treatment [1]. Ultimately the goal of treatment is cure following primary therapy, but it is necessary to refine salvage treatment regimens for those women who have recurrent disease.

Maintenance or consolidation chemotherapy has historically been investigated following initial cytoreductive surgery and postoperative chemotherapy with the intention of evaluating whether extended therapy can lead to improvements in survival. A recent meta-analysis did not show maintenance therapy with platinum agents, paclitaxel, or doxorubicin following primary treatment conferred a survival advantage [2]. However, this meta-analysis did not include studies evaluating the role of PLD. Due to the potential benefit of maintenance therapy studies examining the effects of different agents have reported promising results [3–5]. One of those agents, pegylated liposomal doxorubicin (PLD), has been shown to be well tolerated and to have potential survival benefit when used as consolidation therapy [3, 6].

There have been several recent investigations into optimal therapy for platinum-sensitive recurrent epithelial ovarian cancer [4, 8–14]. Strong evidence has emerged in favor of the combination regimen of carboplatin and pegylated liposomal doxorubicin (PLD) over a carboplatin and paclitaxel regimen as the salvage regimen for platinum-sensitive recurrent ovarian cancer due to its more favorable toxicity profile [12, 14, 15]. Based on its activity, favorable toxicity and availability, we hypothesized that PLD may have a role as maintenance therapy for recurrent ovarian cancer.

The objective of this study was to evaluate the toxicity and effectiveness of maintenance PLD following salvage therapy in women with platinum-sensitive recurrent epithelial ovarian cancer.

Materials and methods

Eligibility

Institutional Review Board approval at the University of Southern California was obtained for this study. All patients receiving PLD maintenance therapy for platinum-sensitive recurrent epithelial ovarian cancer during treatment by the gynecologic oncology or medical oncology services at Los Angeles County Medical Center and Norris Comprehensive Cancer Center between January 1, 2005 and December 31, 2015 were identified. This starting point was chosen based on that the PLD use was approved in late 2014 for recurrent ovarian cancer treatment.

Patient identification was performed via a review of institutional surgical databases (CAFE, Common Application Framework Extensible). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used to outline this retrospective study [16]. Consolidated Standards Of Reporting Trials (CONSORT) diagram was used to outline the study population.

Inclusion criteria were patients with platinum-sensitive recurrent epithelial ovarian, fallopian tubal or primary peritoneal cancer who received PLD as the first maintenance agent following completion of salvage chemotherapy administered for their first recurrent disease. Patients receiving all salvage regimens were included. Exclusion criteria included other types of malignancy diagnoses, platinum-resistant or -refractory disease, recurrence subsequent to the first, or absence of PLD as a maintenance agent. Furthermore, patients that received PLD maintenance as combination therapy or not as the first agent used following completion of salvage chemotherapy were excluded.

Clinical information

Clinical information on the variables collected was gathered via a detailed physician-performed chart review. Variables included demographic information, such as age at diagnosis and ethnicity. Disease-related data included cancer stage and histology from surgical specimens.

Primary treatment-related variables were collected including surgical data, such as date of debulking surgery, components of debulking procedure, surgical complications, and cytoreductive status or residual disease. Details of primary chemotherapy including regimen, number of cycles, and date of completion of platinum agent were documented. Recurrence location and timing was extracted based on clinician notes, lab values, and review of imaging. Timing of initiation and completion, components of, and response to salvage regimen and maintenance PLD administration were collected via a review of physician notes, infusion center records, and pharmacy orders.

Details of PLD maintenance including time interval from completion of primary therapy to initiation of maintenance therapy, number of cycles, starting dose, dosing frequency, dose reductions or spacing, total cumulative dose of PLD received, duration of follow-up after PLD initiation, toxicity information, and the indication for termination of maintenance therapy. Standard PLD maintenance regimen dosing was defined as 40 mg/m^2 administered intravenously every 4 weeks.

Toxicity information was collected via clinical notes; grade of toxicity, if not directly specified, was imputed based on a detailed review of physician exam notes, laboratory values, and management strategy. Toxicity was graded based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTC-AE) version 4.0.

Study definition

Complete cytoreduction was defined at no gross disease at primary surgery, whereas optimal cytoreduction was defined as residual tumor of 1 cm or smaller. Suboptimal cytoreduction was defined as residual tumor size greater than 1 cm. Platinum-sensitive recurrent disease was defined as an ovarian cancer recurrence greater than 6 months following last administration of platinum chemotherapy. In our institutions, baseline cardiac function is usually evaluated either by multigated acquisition scan or echocardiogram prior to the initiation of PLD, and repeat evaluation is indicated based on subjective cardiovascular symptoms.

Progression-free survival was defined as the interval between the first administration of PLD maintenance therapy and the first documentation of disease progression or death resulting from ovarian cancer. Overall survival after recurrence was defined as the interval between the initiation of PLD maintenance therapy and death from any cause. Patients were censored based on the last visit documented in the electronic medical record if they were alive or lost to follow-up. In our practice pattern, serum CA-125 levels are obtained prior to the initiation of each cycle, and systemic imaging is indicated when recurrence or progression is suspected subjectively or objectively.

Study objectives

The primary endpoint of the study was progression-free survival of PLD maintenance therapy after the salvage chemotherapy for platinum-sensitive recurrent epithelial ovarian cancer. Information on overall survival was collected as a secondary endpoint. Toxicity data were also examined as a secondary endpoint.

Statistical consideration

Analysis was performed according to intention to treat. Data were summarized using standard descriptive statistics. Swimmer plot was constructed to depict the time interval between the primary surgery and the last follow-up, and Spearman's correlation coefficient between the PLD maintenance period and other time fragment such as platinum-free interval or time after the completion of PLD maintenance was assessed (two-tailed hypothesis). As the PLD maintenance is relatively infrequent in our practice, sample size justification was estimated as < 30 cases. Thus, analytic approach with multivariate model was deferred in plan for this study. Survival curves were constructed using the Kaplan–Meier method [17]. Statistical Package for Science Software (IBM SPSS, version 24.0, Armonk, NY, USA) was used for the analysis.

Results

Three hundred and twenty-nine patients with suspected epithelial ovarian cancer were initially identified in the database; of those, 296 had histopathologically confirmed epithelial ovarian cancer. Seventy-eight patients did not have records that were sufficiently detailed for data extraction including lost to follow-up. Documented recurrence was

Table 1 Patient demographics

Characteristics	*N* = 28 (100%)
Age (years)	56 (range 35–68)
< 60	18 (64%)
≥ 60	10 (35%)
Race	
Caucasian	7 (25%)
African	1 (3%)
Hispanic	15 (53%)
Asian	2 (7%)
Others	3 (11%)
Stage	
I	0
II	0
III	21 (75%)
IV	7 (25%)
Histology types	
High-grade serous	27 (96%)
Mixed	1 (4%)
Cytoreduction status	
Complete	10 (36%)
Optimal	14 (50%)
Suboptimal	2 (7%)
Unknown	2 (7%)
Platinum-free interval (months)	14 (range 7–63)
< 12	10 (36%)
12.0–17.9	9 (32%)
≥ 18	9 (32%)
Postop chemotherapy	
Carboplatin + paclitaxel	28 (100%)
Recurrence site	
Peritoneum/ascites	14 (50%)
Retroperitoneal lymph nodes	5 (18%)
Pelvic/abdominal mass	5 (18%)
Pulmonary/thoracic	4 (14%)
2nd cytoreduction*	
Yes	4 (14%)**
No	24 (86%)

IQR interquartile range, *PLD* pegylated liposomal doxorubicin

*For recurrent cases

**2 complete, 1 optimal, and 1 suboptimal

seen in 113 of the remaining patients, and, of those, 66 had platinum-sensitive recurrent disease. After excluding cases with progressive disease on salvage therapy, 28 received maintenance with PLD and thus fulfilled inclusion criteria (Supplemental Figure S1).

Demographic and disease characteristics are detailed in Table 1. The median age was 56 (range 35–68) and 18 (64%) women included were under the age of 60 years. The majority of women were Hispanic ($n=15$, 53%) followed by White/Caucasian ($n=7$, 25%).

All patients were diagnosed with advanced-stage disease at the primary diagnosis [stage III $n=21$ (75%), and stage IV $n=7$ (25%)]. High-grade serous histology composed the vast majority ($n=27$, 96%), whereas one patient had mixed histology. All patients underwent tumor reductive surgery as part of their primary treatment. In terms of cytoreductive status at time of primary cytoreduction, 10 (36%) were classified as complete, 14 (50%) as optimal, and 2 (7%) were suboptimal.

All patients received carboplatin and paclitaxel as their primary treatment regimen (100%). The median platinum-free interval prior to the first recurrence was 14.0 months (range 7.0–63.0). Nine (32%) patients had a platinum-free interval extending greater than 18 months. The majority of recurrences were diagnosed based on peritoneal nodule and/or malignant ascites ($n=14$, 50%). Other recurrence sites included retroperitoneal lymph nodes ($n=5$, 18%), pulmonary or thoracic disease ($n=4$, 14%), and a pelvic or abdominal mass ($n=5$, 18%). Four (14%) patients were treated with secondary cytoreduction at the time of recurrence. Of these, two (50%) resulted in complete cytoreduction while the remaining surgeries were classified as either optimal ($n=1$, 25%) or suboptimal ($n=1$, 25%).

Details of PLD maintenance following salvage chemotherapy can be found in Table 2. Following the first recurrence, the majority of women received carboplatin and PLD as a salvage regimen ($n=20$, 71%). Less frequent salvage regimens included carboplatin plus gemcitabine ($n=5$, 18%), and carboplatin plus paclitaxel ($n=1$, 4%). Twelve (43%) women demonstrated a partial response on imaging following salvage chemotherapy, while 11 (39%) had a complete response, 4 (14%) had stable disease, and 1 (4%) had progressive disease.

Median PLD cycle number was 7.5 (range 2–26), with 11 (40%) women received ≥12 cycles. While rare, some women received greater than 24 cycles ($n=3$, 11%). The median total cumulative dose of PLD was 432.5 mg/m^2 (range 120–1200 mg/m^2). Maximum cumulative PLD dose was 1200 mg/m^2. Discontinuation of PLD maintenance was most often attributed to progressive disease ($n=16$, 57%), while toxicity/side effects ($n=3$, 11%), and patient preference ($n=7$, 25%) were cited as reasons for cessation of maintenance PLD.

Table 2 Pegylated liposomal doxorubicin treatment

Characteristics	$N=28$ (100%)
Salvage regimen	
Carboplatin + PLD	20 (71%)
Carboplatin + paclitaxel	1 (4%)
Carboplatin + gemcitabine	5 (18%)
Other regimens	2 (7%)
PLD cycle	7.5 (range 2–26)
<6	11 (39%)
6–11	6 (21%)
12–17	5 (18%)
18–23	3 (11%)
≥24	3 (11%)
PLD total dose	432.5 (range 120–1,200)
<300 mg/m^2	8 (29%)
300–599	11 (39%)
≥600	9 (32%)
Response*	
Complete	11 (39%)
Partial	12 (43%)
Stable	4 (14%)
Progressive	1 (4%)
Reason for discontinuation	
Progressive disease	16 (57%)
Toxicity/side effects	3 (11%)
Patient preference	7 (25%)
Other	2 (7%)

IQR interquartile range, *PLD* pegylated liposomal doxorubicin

*Response was determined via imaging at the completion of salvage therapy. Although salvage cycle number varied, 6 cycles of salvage chemotherapy was most common amongst our patient population

Toxicity characteristics are available in Table 3. Sixteen ($n=16$, 57%) of women reported any grade of adverse effects, including 3 (11%) women with grade 3 toxicity. No grade ≥4 toxicity was noted. The most common toxicities documented were mucositis/stomatitis ($n=7$, 25%), palmar–plantar erythrodysesthesia ($n=6$, 21%), and myelosuppression ($n=3$, 11%). No evidence of cardiotoxicity or transaminitis was identified in this cohort. The majority of toxicities were grade 1 ($n=7$, 25%), with the remaining being grade 2 ($n=4$, 14%) and grade 3 ($n=3$, 11%). Two (7%) toxicity events did not have a grade specified nor enough clinical detail available to impute a grade through chart review.

The vast majority of toxicities were well managed with a dose reduction ($n=14$, 50%). Cycle spacing to every 5 weeks ($n=2$, 7%) or a break in treatment of greater than 4 weeks ($n=2$, 7%) also successfully reduced toxicity and enabled continuation of the maintenance regimen. The majority of dose reductions occurred early in the maintenance regimen,

Table 3 Toxicity related to PLD maintenance therapy

Any toxicity/side effects reported*	$n=16$ (100%)
Toxicity classification	
Mucositis/stomatitis	7 (44%)
PPE	6 (38%)
Myelosuppression	3 (19%)
Other	1 (6%)
Cardiotoxicity	0
Transaminitis	0
Toxicity grade	
1	7 (44%)
2	4 (25%)
3	3 (19%)
4	0 (0%)
Unspecified	2 (13%)
Toxicity management	
Dose reduction	14 (88%)
Cycle spacing to 5 weeks	2 (13%)
PLD holiday	2 (13%)
Dose reduction following PLD cycle	
0–5	10 (71%)
6–10	2 (14%)
11–15	2 (14%)
> 15	0
Dose after reduction	
35 mg/m^2	6 (43%)
30 mg/m^2	8 (57%)
< 30 mg/m^2	0

Number with percentage per 16 patients who developed any grade toxicity. Abbreviations: PLD, pegylated liposomal doxorubicin; PPE, palmar–plantar erythrodysesthesia. *any grades of toxicity. **denominator set at 16 for toxicity calculations

with 10 (36%) women who had reductions occurring prior to the 5th cycle. No dose reductions were required after 15 cycles. The most common dose following dose reduction was 30 mg/m^2 ($n=8$, 29%), followed by 35 mg/m^2 ($n=6$, 21%). No doses less than 30 mg/m^2 were required.

The median follow-up time after the date of the first recurrence among women who were censored was 30.5 months (interquartile range 41.7). There were 20 (71%) total women who had disease progression during the follow-up period including 16 (57%) that progressed through maintenance PLD and an additional 4 (14%) that progressed following discontinuation of PLD due to toxicity; the median progression-free survival was 14.5 months (2- and 5-year progression-free survival rates 21.1% and 15.8%, respectively; Fig. 1). There were 9 (32%) women who died of ovarian cancer during the course of our study. The median overall survival time following the first recurrence was 51.2 months, and 2- and 5-year overall survival rates were 90.7% and 43.4%, respectively. Swimmer plots are displayed in Fig. 2. Platinum-free interval after the

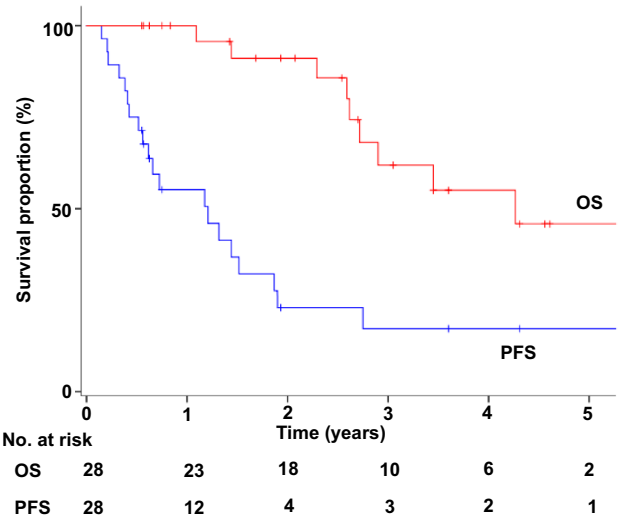

Fig. 1 Kaplan–Meier survival curves. *OS* overall survival after the pegylated liposomal doxorubicin maintenance initiation, *PFS* progression-free survival

primary surgery ($r=0.15$, $P=0.46$) and time duration after the PLD maintenance ($r=0.09$, $P=0.65$) were not associated with the duration of PLD maintenance.

Discussion

The results of this study indicate a potential role for maintenance PLD for platinum-sensitive recurrent epithelial ovarian cancer patients. Overall, the median progression-free survival of 14.5 months and overall survival after the initiation of PLD maintenance of 51.2 months over a median follow-up period of 30.5 months suggests that PLD may compare favorably to recent reports evaluating the role of novel targeted agents. Moreover, PLD maintenance was generally well tolerated, and the predominantly low-grade toxicity events that occurred were managed well with minor dose adjustments. Furthermore, PLD is a more affordable option than some of the newer biologics and anti-angiogenic therapies being trialed as maintenance agents [7].

Since the majority of advanced-stage epithelial ovarian cancers will ultimately recur following the initial treatment, there has been a great deal of interest in seeking salvage or maintenance treatment regimens that prolong survival while preserving quality of life. In addition to traditional chemotherapeutics, several novel agents have also been investigated as salvage or maintenance agents for platinum-sensitive recurrent epithelial ovarian cancer. A summary of recent salient trials of various salvage and maintenance trials for platinum-sensitive recurrent ovarian cancer is shown in Table 4.

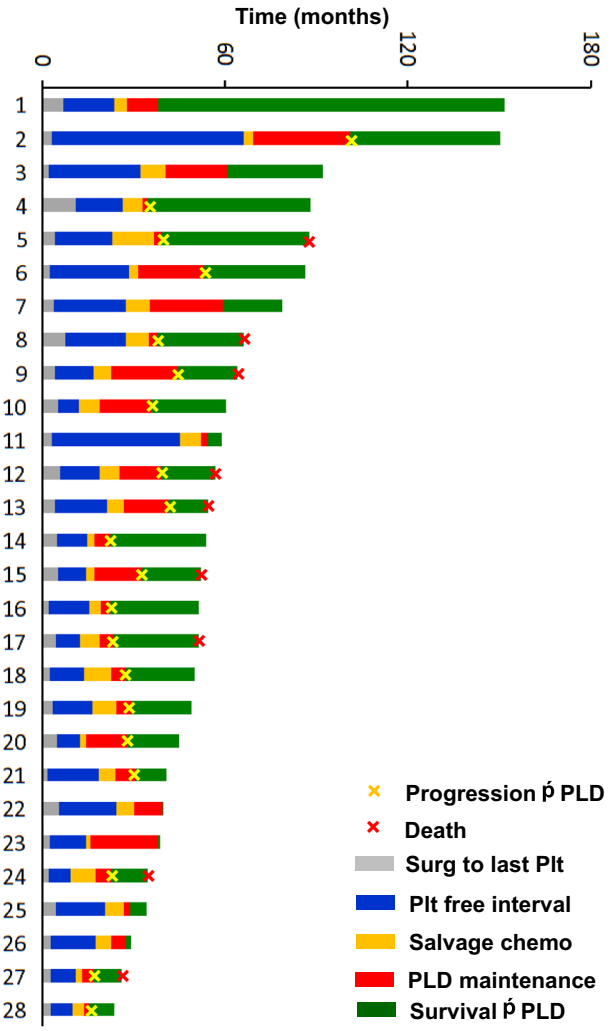

Fig. 2 Swimmer plots for survival time. Time between the primary surgery and the last follow-up is shown based on the treatment and survival events. *PLD* pegylated liposomal doxorubicin maintenance, *Plt* platinum, ṕ after

PLD has been shown to be an effective agent for platinum-sensitive recurrent epithelial ovarian cancer in several of these trials; such as, the CALYPSO trial, which demonstrated the non-inferiority of a platinum doublet consisting of carboplatin and PLD when compared to carboplatin and paclitaxel [12, 15]. There have also been recent investigations into the role of anti-angiogenics in the treatment of platinum-sensitive recurrent epithelial ovarian cancers. While none of these have directly compared survival and toxicity outcomes with those of PLD, our preliminary data suggest PLD might have comparable survival outcomes with fewer high-grade toxicity complications when compared anti-angiogenic agents, such as bevacizumab (progression-free survival ranges 12.4-13.8 versus 14.5 months for current study) [8, 9, 13, 18].

Recently various poly (ADP-ribose) polymerase inhibitors (PARPi) have demonstrated high activity in recurrent ovarian cancer. Of interest, a randomized trial evaluating the efficacy of PLD and olaparib in patients with BRCA mutations and recurrent ovarian cancer showed no statistically significant difference in PFS or response [19]. PARPis have been especially successful in prolonging disease-free survival in carriers of BRCA mutations and presence of homologous recombination deficiency (HRD) [10, 19, 20]. It has been noted previously that patients with HRD or mutations causing HRD, such as somatic BRCA1/2 deficiency, respond especially well to anthracycline-based chemotherapeutics, such as PLD [21].

Although the exact mechanism for this observation is unknown, it is possible that immunogenic cell death from anthracyclines may result in enhanced immune response and a therefore robust physiologic anti-tumor activity. Notably, there is an ongoing phase II clinical trial examining the efficiency of a combination of PLD with a checkpoint inhibitor, pembrolizumab, in platinum-resistant recurrent epithelial ovarian cancer [22]. Comparing the effectiveness of PLD maintenance to PAPRi maintenance amongst patients with BRCA mutations or HRD is beyond the scope of this paper, but is an intriguing question to be addressed in future studies.

A comparison of toxicity data amongst relevant studies can be found in Table 4. The toxicity profile for PLD maintenance was relatively favorable when compared to alternative agents. Although toxicity events in this study were common, they were easily managed with dose reductions or extensions that enabled continued administration of PLD maintenance. Toxicities reported in this study were those typically associated with PLD including mucositis, stomatitis, palmar–plantar erythrodysesthesia, and myelosuppression. Notably, there were no reports of cardiotoxicity. Additionally, grade 3 toxicity events were rare (20%) while no grade 4–5 toxicity events occurred.

One concern with higher doses of certain chemotherapeutics and biologics is that of increased risk of secondary primary malignancy, and this risk should be considered in the dosing of maintenance agents since these are intended to be administered for an extended number of cycles. Although PLD is well tolerated long-term, there have been multiple reports of the development of squamous cell carcinomas of the oral cavity in patients that were on maintenance PLD [23]. Furthermore, there is some concern that patients with BRCA mutations are more susceptible to squamous cell carcinomas, thus suggesting that greater surveillance may be warranted in women with BRCA haploinsufficiency [23]. The range of cumulative doses of PLD amongst the patients with presumed chemotherapy-related squamous cell carcinomas was 720 to almost 4,000 mg/m^2; the median dose was 2,116 mg [23, 24]. Providers prescribing high doses of

Table 4 Review of the recent literature on platinum-sensitive recurrent ovarian cancer

Study name/ author	**Experimental/** control agents[a]	Maintenance agent	PFS (months)	OS (months)	Overall toxicity[d,c]	Grade 3–4 toxicity[c]	Primary toxicities[c]
CALYPSO Pujade-Lauraine [12, 15]	**Carboplatin/ PLD** vs carboplatin/ paclitaxel	None	**11.3** vs 9.4	**30.7** vs 33.0	80%	28.4%	Neutropenia (79.6%) Anemia (66.3%) Fatigue (77.9%) PPE (38.6%)
Kaye[b] [19]	PLD vs **olaparib** (400 mg)	None	**8.8** vs 7.1	Not reported/ inconclusive	30%	13%	Nausea (78%) Fatigue (65%) Emesis (50%)
Ledermann [4]	Platinum doublet	**Olaparib** vs placebo	**8.4** vs 4.8	**29.7** vs 29.9	95.6%	35.3%	Nausea (68%) Fatigue (49%) Emesis (32%) Anemia (17%)
OCEANS Aghajanian [8, 9]	Carboplatin/ paclitaxel ± **bevacizumab**	Possible **bevacizumab**	**12.4** vs 8.4	**33.6** vs 32.9	100%	89.5%	Hypertension (17.4%) Proteinuria (8.5%) Neutropenia (20.6%)
NOVA Mirza [10]		**Niraparib** vs. placebo	**21.0 (gBRCA) vs 12.9 (HRD) vs 9.3 (ITT)** vs. 3.9	Not yet matured	100%	74%	Nausea (73.6%) Thrombocytopenia (61.3%) Fatigue (59.4%) Anemia (50.1%)
SOLO2[b] Pujade-Lauraine [20]		**Olaparib** vs placebo	**19.1** vs 5.5	Not yet matured	98%	36%	Nausea (73%) Fatigue (62%) Vomiting (35%)
GOG 213 Coleman [18]	Carboplatin/ paclitaxel ± **bevacizumab**	**Bevacizumab**	**13.8** vs 10.4	**42.2** vs 37.3	96%	30%	Non-CNS bleeding (42%) Hypertension (41%) Proteinuria (17%)
ARIEL3 Coleman [30]		**Rucaparib** vs placebo	**16.6 BRCAmut) vs 13.6 (HRD) vs 10.8 (ITT)** vs 5.4	Not yet matured	100%	56%	Nausea (75%) Fatigue (69%) Dysgeusia (39%) Anemia (37%)
Blake[e]		**PLD**	**14.5**	**51.2**[f]	58%	50%	Mucositis/stomatitis (47%) PPE (33%) Myelosuppression (20%)

[a]Experimental agent indicated in bold. PFS and OS associated with the experimental agent also indicated in bold

[b]Indicates studies enrolling only women with BRCA1/2 mutations

[c]All toxicity data are in reference to experimental arm

[d]Overall toxicity was defined as any toxicity grade for the experimental study arm but not for the placebo arm

[e]Included as a comparator, does not represent a randomized controlled trial so direct comparison is not appropriate

[f]Overall survival is defined as the interval between the start date of PLD maintenance therapy to death from any cause

PLD pegylated liposomal doxorubicin, *PPE* palmar–plantar erythrodysesthesia, *PFS* progression-free survival, *OS* overall survival, *BRCAmut* BRCA mutated carcinoma, *gBRCA* germline BRCA mutation, *ITT* intention to treat, *HRD* homologous recombination deficiency

PLD should be aware of this rare complication and ensure oral screening take place during visits with the awareness that new-onset leukoplakia can be a precursor to malignancy.

As the cost of treatments for malignancy gains increasing attention, it is important to make financially informed treatment decisions for all patients [25]. Although the cost incurred by patients will vary based on their insurance coverage, the costs to the overall healthcare system of each individual drug remain fairly constant. Currently, the cost of novel agents such as PARP inhibitors and anti-angiogenics

far exceeds that of traditional intravenous chemotherapeutics (Supplemental Table S1). Recent studies of individual PARP inhibitors have not shown them to be cost effective as maintenance agents in platinum-sensitive recurrent epithelial ovarian cancer, with the exception of olaparib for patients with recurrent disease in the setting of germline BRCA mutations [26–28]. Therefore, if PLD were shown to be an equally effective but more affordable alternative, use of this agent in treating recurrent disease would contribute to decreasing the economic burden of cancer care on the healthcare system.

Last, based on the statistics of our study results, the initiation dose of maintenance PLD can be at 30–35 mg/m^2 instead of 40 mg/m^2 because of high prevalence of dose reduction (50%). This is most likely that women with recurrent ovarian cancer have received multiple lines and cycles of chemotherapy prior to the PLD maintenance, making patients sensitive to higher dose of PLD with 40 mg/m^2.

Strengths of this study include that it provides detailed analysis that enables a comprehensive description of the effectiveness and toxicity of PLD as a maintenance agent. Additionally, this is the largest case series analysis of PLD as a maintenance agent for platinum-sensitive recurrent epithelial ovarian cancer.

A salient weakness of this study is the lack of a control group. In our study population, there were seven women who did not receive maintenance PLD after responded to the first-line salvage chemotherapy for platinum-sensitive recurrent disease (Supplemental Figure S1). We were not able to abstract the information regarding the counseling/discussion for PLD maintenance. One woman received bevacizumab maintenance. The median progression-free survival of this group was 24 months and there were four (57.1%) women who developed disease progression and one (14.3%) woman who died of disease. Thus, limited number and lack of detailed information made us unable to conduct an intergroup comparison between who received PLD maintenance and those who did not.

In addition, bias inherent in the retrospective design allows for confounding factors that cannot be accounted for. An additional weakness is that the data remain reliant on a platinum-sensitive paradigm and does not include information on genetic or molecular abnormalities [29]. Comparison to historical trials is also challenging as the starting point for survival measurement varies across the studies (e.g., maintenance starting date versus chemotherapy starting date).

Overall, this study indicates that PLD maintenance treatment for platinum-sensitive recurrent epithelial ovarian cancer has the potential for promising improvements in survival. In this study, PLD maintenance therapy compared favorably to other consolidation strategies in prolonging progression-free survival and overall survival. Further investigation of this agent for maintenance following salvage treatment, especially with randomized controlled design, could provide an affordable and relatively well-tolerated option for women with recurrent, platinum-sensitive ovarian cancer.

Author contributions E.A. Blake: data curation, project administration, validation, writing (original draft). C.A. Bradley: project administration, writing (original draft). S. Mostofizadeh: data curation, project administration, writing (review/editing). F.M. Muggia: conceptualization, supervision, writing (review/editing). A.A. Garcia: conceptualization, investigation, writing (review/editing). L.D. Roman: conceptualization, funding acquisition, resources, supervision, writing (review/editing). K. Matsuo: conceptualization, formal analysis, funding acquisition, investigation, methodology, software, supervision, validation, visualization, writing (review/editing).

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Compliance with ethical standards

Conflict of interest Consultant, Tempus Labs (L.D.R.); honorarium, Chugai, book editorial, Springer, and meeting expense, OVAL (K.M.); none related to this study.

Ethical approval The study involving human participants performed by authors is approved by Institutional Review Board, University of Southern California.

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