The Role of Pegylated Liposomal Doxorubicin in Ovarian Cancer: A Meta-Analysis of Randomized Clinical Trials

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Pegylated liposomal doxorubicin • Ovarian cancer • Meta-analysis • Carboplatin • Paclitaxel

Learning Objectives

Determine circumstances under which ovarian cancer patients would benefit from carboplatin plus pegylated liposomal doxorubicin rather than carboplatin plus paclitaxel.

Compare and contrast efficacy and toxicity profiles of carboplatin plus pegylated liposomal doxorubicin versus carboplatin plus paclitaxel.

Compare and contrast efficacy and toxicity profiles of single agent pegylated liposomal doxorubicin versus topotecan, gemcitabine, olaparib, patupilone, and canfosfamide.

ABSTRACT

Background. Recent studies suggest that carboplatin with pegylated liposomal doxorubicin (C+PLD) is as efficacious as carboplatin with paclitaxel (C+P) and possibly is more tolerable for ovarian cancer therapy. Pegylated liposomal doxorubicin (PLD) may also be efficacious and tolerable as monotherapy in recurrent or platinum-resistant disease. We performed a meta-analysis of randomized trials in order to elucidate the role of PLD in ovarian cancer.

Methods. We searched PubMed, Scopus, and ISI Web of Knowledge for studies comparing C+PLD with C+P and comparing PLD with another monotherapy. Summary hazard ratios (HRs) and relative risks with their corresponding 95% confidence intervals (CIs) were calculated using a fixed-effects model.

Results. Three trials were included in the doublet regimen analysis, and five trials were included in the monotherapy regimen analysis. C+PLD provided superior progression-free sur-

vival (PFS) (HR, 0.87; 95% CI, 0.78–0.96) and similar overall survival (OS; HR, 0.95; 95% CI, 0.84–1.07) compared with C+P. There was no evidence of improved tolerability: C+PLD had more gastrointestinal toxicity, anemia, thrombocytopenia, cutaneous toxicity, and mucositis/stomatitis, although there was less neutropenia, neuropathy, and alopecia. PLD monotherapy had similar PFS (HR, 0.99; 95% CI, 0.89–1.11) and OS (HR, 0.99; 95% CI, 0.88–1.11) to other monotherapies, but it was more tolerable. There was less neutropenia, anemia, thrombocytopenia, and gastrointestinal toxicity, although cutaneous toxicity was increased.

Conclusion. C+PLD had better PFS and similar OS compared with C+P and had a very different toxicity profile. Therapy selection could be based on patient risks for side effects. PLD is as efficacious as other monotherapies and is more tolerable. *The Oncologist* 2013;18:1022–1031

Implications for Practice: Carboplatin with paclitaxel (C+P) has been the standard first-line chemotherapy regimen for ovarian cancer patients; however, two large randomized trials of carboplatin and pegylated liposomal doxorubicin (C+PLD) versus C+P suggest that C+PLD is as efficacious as C+P and possibly is more tolerable. The results of our analysis showed that C+PLD has better progression-free survival than C+P and similar overall survival; however, we did not find C+PLD to be more tolerable than C+P. The toxicity profiles were very different, and therapy selection could reasonably be based on individual patient risks of side effects. Pegylated liposomal doxorubicin (PLD) is also a treatment option for recurrent or platinum-resistant ovarian cancer, but there is no clear distinction among any of the monotherapy options in this setting. The results of our analysis showed that PLD is as efficacious as other monotherapies and is more tolerable. Consequently, it may be the preferred agent in the palliative setting.

INTRODUCTION

Ovarian cancer is the leading cause of death from gynecologic malignancies in the United States [1]. Standard first-line treatment includes surgical debulking and platinum-based chemo-

therapy, usually consisting of carboplatin with paclitaxel (C+P). However, only 40%–60% of patients will achieve complete remission, and less than 40% of women with ovarian

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cancer are ever cured [1, 2]. In addition, this regimen has high rates of neurotoxicity, which can persist more than a year after completion of treatment [3, 4]. Consequently, it is important that more efficacious or tolerable options are identified. One such alternative agent is pegylated liposomal doxorubicin (PLD), an anthracycline encapsulated within a sterically stabilized liposome. Delivery of doxorubicin by this pegylated liposomal carrier increases the agent's circulating half-life from approximately 3 hours to 55 hours and alters its toxicity profile [5]. PLD is reported to be associated with significantly less cardiac toxicity and myelosuppression than conventional doxorubicin; however, it was associated with more mucositis and palmar-plantar erythrodysesthesia (also known as "hand-foot syndrome") [6].

Recent clinical trials suggest that combination therapy consisting of carboplatin with PLD (C+PLD) may have similar or better rates of progression-free survival (PFS) and similar overall survival (OS) when compared with C+P, the current first-line regimen [7–10]. In addition, it was suggested that PLD had a more favorable toxicity profile than C+P [7], but these findings were not always corroborated in other clinical trials [9, 11]. There is a need to clarify the efficacy and toxicity profiles of C+PLD compared with C+P in order to facilitate therapeutic decision making and optimize patient outcomes.

Monotherapy options are typically used after failing therapy with C+P in cases where there is evidence of platinum resistance. Single-agent therapies include PLD, gemcitabine, etoposide, topotecan, vinorelbine, and bevacizumab [1, 2]. There are no clear differences in PFS or OS among any of the therapies [12], although one trial reported more favorable OS with PLD compared with topotecan [13]. There are an increasing number of therapeutic options for recurrent or platinum-resistant ovarian cancer. Recently, patupilone, an epothilone microtubule inhibitor, was directly compared with PLD and showed similar PFS and OS in patients with recurrent or refractory ovarian cancer [14]. Among the monotherapy options, PLD appears promising because it may be more tolerable than some of the other agents. In particular, PLD was associated with better health-related quality of life (QOL) in comparison with gemcitabine [15]; however, it is not clear whether PLD compares favorably with the other agents. There is a need to clarify the efficacy and toxicity profiles of PLD in this setting to facilitate therapy selection.

In order to elucidate the role of PLD in the treatment of ovarian cancer, we conducted this meta-analysis of randomized clinical trials to evaluate the efficacy and the toxicity of (a) a platinum-based regimen containing PLD compared with a platinum-based regimen containing a taxane and (b) PLD as a single agent compared with other single-agent regimens in the treatment of ovarian cancer. The results of our study will help inform therapy selection for the treatment of ovarian cancer.

METHODS

Literature Search

A systematic literature search of electronic databases (PubMed, 1997–2013; ISI Web of Knowledge, 2001–2013; and Scopus, 1999–2013) was performed. The terms for the search strategy were "pegylated liposomal doxorubicin" and "ovarian cancer." There were no language restrictions. The full

search is available on request. The reference lists of review articles and included studies were hand searched to identify additional potentially eligible studies.

Inclusion and Exclusion Criteria

For the meta-analysis evaluating the efficacy and toxicity of a platinum-based doublet regimen, all randomized controlled trials comparing a treatment arm containing a platinum agent with PLD versus a treatment arm containing a platinum agent with a taxane in patients with histologically confirmed ovarian cancer were potentially eligible. For the meta-analysis evaluating the efficacy and toxicity of monotherapy regimens, all randomized controlled trials comparing a treatment arm of single-agent PLD versus a treatment arm containing any other cytotoxic monotherapy in patients with histologically confirmed ovarian cancer were potentially eligible. Trials were potentially eligible regardless of line of treatment. Trials published in abstract form only were excluded because of the lack of efficacy and toxicity data. Assessment of eligibility criteria were performed independently by three investigators. Differences were resolved by consensus.

Data Extraction

Extraction of study characteristics and adverse event data from the text, tables, and figures of included studies was performed independently by three investigators, and differences were resolved by consensus. Study characteristics (first author, journal, year of publication), trial design characteristics (study design, outcome measurement, type of cancer, therapy regimen for each arm), study population (median age, number of patients evaluated for efficacy and safety endpoints in each arm), efficacy results (hazard ratios [HRs] and 95% confidence intervals [CIs] for survival data), and adverse event results (type and number of adverse events in each treatment arm) were recorded. Several trials did not provide an HR or a CI for survival data, in which case two investigators independently analyzed the trials' Kaplan-Meier curves to calculate these data using the method described by Parmar et al. [16]. The adverse event "GI toxicity" was obtained by combining the events for nausea, vomiting, constipation, and diarrhea. In the meta-analysis of the monotherapy regimens, this category also included abdominal pain and abdominal cramping. "Neuropathy" was obtained by combining the events for sensory neuropathy, motor neuropathy, general neuropathy, and neurotoxicity.

Statistical Analysis

For survival variables such as OS and PFS, we used the HR and the corresponding 95% CI, which are presented as forest plots. For categorical variables, we used the risk ratio (RR) and the corresponding 95% CI, which are presented as forest plots. The results were tested for heterogeneity and were considered significant for a p value $< .05$, in accordance with the random-effects model developed by DerSimonian and Laird [17]. We used the fixed-effect model because there was no evidence of heterogeneity among the studies. Meta-analysis was conducted using the Comprehensive Meta-Analysis software (Biostat, Englewood, NJ, <http://www.meta-analysis.com/>).

Figure 1. Selection process of eligible studies for trials comparing doublet regimens.
^aOne trial excluded because progression-free survival was not reported.
Abbreviations: PLD, pegylated liposomal doxorubicin; PFS, progression-free survival; OS, overall survival.

Figure 2. Selection process of eligible studies for trials comparing monotherapy regimens.
^aData from one trial were reported as time to progression, which was used as a surrogate for progression-free survival.
Abbreviations: PLD, pegylated liposomal doxorubicin; PFS, progression-free survival; OS, overall survival.

RESULTS

Literature Search

The search yielded 233 publications. Published abstracts were reviewed, and the articles were excluded from further evaluation if their treatment arms did not meet the inclusion criteria for the meta-analysis, the publications were subset analyses, or the publications were preliminary or duplicate reports of the same trial. To ensure that no new publications were missed during or after screening, notifications from PubMed were used to identify eligible new studies.

Three trials met the inclusion criteria in the meta-analysis of efficacy and toxicity of a platinum-based regimen with PLD versus a platinum-based regimen with a taxane (Fig. 1). All three trials compared C+PLD versus C+P.

Five trials met the criteria for inclusion in the meta-analysis of the efficacy and toxicity of single-agent PLD versus another monotherapy (Fig. 2). From these trials, six comparator cohorts were identified: two cohorts for gemcitabine, two cohorts for topotecan, one cohort for canfosfamide, and one cohort for patupilone. The canfosfamide cohort and one of the two topotecan cohorts were from the same two-arm trial comparing canfosfamide with PLD or topotecan.

Study Characteristics

The trials included in the C+PLD versus C+P meta-analysis were all randomized multicenter studies, and study characteristics are summarized in Table 1. CALYPSO [18] and MITO-2 [9] were phase III trials, whereas Hellenic [10] was a phase II trial. Overall, a total of 970 patients were treated with C+PLD, and 1,015 patients were treated with C+P. All patients in these three trials had platinum-sensitive ovarian carcinoma. Pa-

Table 1. Characteristics of included studies

Trial or cohort (year published)	Treatment	No. of patients	Type of trial	Age (years)	Patient characteristics	Pretreatment status	Outcomes reported
CALYPSO [19] (2012)	C + P	509	Randomized, multicenter, phase III	61	Platinum-sensitive ovarian carcinoma, fallopian tube carcinoma, and extraovarian papillary serous tumor	Disease progression after first- or second-line platinum- and taxane-based chemotherapy	PFS, toxicity, QOL, OS
	C + PLD	467		60.5			
MITO-2 [9] (2011)	C + P	410	Randomized, multicenter, phase III	57	Platinum-sensitive epithelial ovarian carcinoma	Chemotherapy naïve	PFS, OS, treatment activity, toxicity, QOL
	C + PLD	410		57			
Hellenic [10] (2010)	C + P	96	Randomized, multicenter, phase II	63	Platinum-sensitive recurrent ovarian carcinoma	One cycle or more of platinum-based chemotherapy	Relative risk and toxicity, TTP, OS
	C + PLD	93		62			
Gemcitabine I [16] (2008)	Gemcitabine	77	Randomized, multicenter, phase III	63	Platinum-sensitive recurrent epithelial ovarian carcinoma	Failed first-line platinum/paclitaxel chemotherapy	TTP, OS, response rate, toxicity, QOL
	PLD	76		63			
Gemcitabine II [21] (2007)	Gemcitabine	99	Randomized, multicenter, phase III	59	Platinum-resistant epithelial ovarian carcinoma, fallopian tube carcinoma, primary peritoneal carcinoma	Prior platinum-based chemotherapy required, ≤ 2 prior regimens allowed	PFS, tumor response, time to treatment failure, OS, QOL
	PLD	96		62			
Topotecan I [22] ^a (2009)	Topotecan	87	Randomized, multicenter, phase III	NR	Platinum-resistant advanced epithelial ovarian carcinoma, fallopian tube carcinoma, peritoneal carcinoma	Failed one second-line therapy with either topotecan or PLD	Toxicity ^b
	PLD	130		NR			
Topotecan II [13] (2004)	Topotecan	239	Randomized, multicenter, phase III	60	Mixed platinum sensitivity with recurrent epithelial ovarian carcinoma	Failed first-line, platinum-based chemotherapy	PFS, OS, response rate, duration of response, toxicity
	PLD	235		60			
Canfosfamide [22] ^a (2009)	Canfosfamide	231	Randomized, multicenter, phase III	60	Platinum-resistant advanced epithelial ovarian carcinoma, fallopian tube carcinoma, peritoneal carcinoma	Failed one second-line therapy with either topotecan or PLD	Toxicity ^b
	PLD	130		NR			
Patupilone [15] (2012)	Patupilone	412	Randomized, multicenter, phase III	59	Platinum-resistant epithelial ovarian carcinoma, primary fallopian tube carcinoma, primary peritoneal carcinoma	Failed ≥ 4 cycles of platinum-based chemotherapy or discontinued because of toxicity	OS, PFS, objective response rate, duration of response, cancer antigen 125, response, toxicity
	PLD	417		59			

^aCanfosfamide and Topotecan I are two cohorts of the same trial comparing canfosfamide with PLD or topotecan.

^bPFS and OS were also reported, but the hazard ratios were based on canfosfamide versus PLD or topotecan; therefore, these results were not included in this meta-analysis.

Abbreviations: C + P, carboplatin and paclitaxel; C + PLD, carboplatin and pegylated liposomal doxorubicin; PLD, pegylated liposomal doxorubicin; NR, not recorded; PFS, progression free survival; QOL, quality of life; OS, overall survival; TTP, time to progression.

tients in CALYPSO and Hellenic were previously treated with C + P, whereas patients in MITO-2 were chemotherapy naïve. The C + P doses in all three trials were the same: carboplatin area under the curve of 5 mg/mL per minute and paclitaxel 175 mg/m² every 3 weeks. The PLD doses varied: Patients in CALYPSO were treated with PLD 30 mg/m² every 4 weeks, patients in MITO-2 received PLD 30 mg/m² every 3 weeks, and patients in Hellenic were given PLD 45 mg/m² every 4 weeks. Trial quality was assessed according to the *Cochrane Handbook for Systematic Reviews of Interventions* [19] (Table 2).

The trials included for the monotherapy regimens were also all phase III, randomized, multicenter trials (Table 1). A total of 954 patients were treated with PLD, and 1,145 patients were treated with an alternative monotherapy agent (176 patients received gemcitabine, 326 patients received topotecan, 231 patients received canfosfamide, and 412 patients received patupilone). All patients had histologically confirmed ovarian carcinoma, but their platinum-sensitivity status differed (Table 1). All PLD cohorts were treated with 50 mg/m² intravenously every 4 weeks, except for one of the trials in which PLD 40 mg/m² was administered intravenously every 4 weeks. The following comparator regimens were used: gemcitabine 1,000 mg/m² on days 1, 8, and 15 every 4 weeks (Gemcitabine I) [15]; gemcitabine 1,000 mg/m² on days 1 and 8 every 3

weeks (Gemcitabine II) [20]; topotecan 1.5 mg/m² intravenously for 5 consecutive days every 3 weeks (both Topotecan I [21] and Topotecan II [13] cohorts); canfosfamide 1,000 mg/m² intravenously every 3 weeks [21]; and patupilone 10 mg/m² intravenously every 3 weeks [14]. Trial quality was assessed according to the *Cochrane Handbook for Systematic Reviews of Interventions* [19] (Table 2).

Extraction of Data

For survival analyses, we used the HR and the 95% CI reported in the literature or calculated from Kaplan-Meier curves [16]. The coefficient of variation of the data calculated independently by two investigators ranged from 0.65% to 6.59%. In the meta-analysis of the combination regimens, the Hellenic trial had incomplete data: no PFS data were reported, and OS was reported as a Kaplan-Meier curve without any HRs. For the toxicity analyses, we used the rates reported in the literature to calculate the RR and the 95% CI of each side effect.

C + PLD Versus C + P

PFS was evaluated in two of the three included trials. Meta-analysis showed that C + PLD was associated with a significant improvement in PFS (HR, 0.87; 95% CI, 0.78–0.96; $p = .008$) (Fig. 3). OS was evaluated in all three trials. Meta-analysis

Table 2. Quality assessment of included studies

Trial or cohort	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Intent-to-treat analysis	Other potential threats
CALYPSO [19]	Random; permuted blocks of 6	Unclear	No	No	No	Yes	Yes
MITO-2 [9]	Random; telephone assignment	Yes	No	No	No	Yes	Yes
Hellenic [10]	Random; telephone assignment	Yes	No	Yes	Yes	No	Yes
Gemcitabine I [16]	Random; telephone assignment	Yes	Evaluators blinded	Yes	Yes	Yes	Yes
Gemcitabine II [21]	Random; unclear	Unclear	No	Yes	Yes	Yes	Yes
Topotecan I [22] ^a	First step randomized; second step not randomized	Unclear	No	Yes	Yes	Yes	Yes
Topotecan II [13]	Random; unclear	Unclear	No	Yes	Yes	Yes	Yes
Canfosfamide [22] ^a	First step randomized; second step not randomized	Unclear	No	Yes	Yes	Yes	Yes
Patupilone [15]	Random; telephone assignment	Yes	Evaluators blinded	Yes	Yes	Yes	Yes

^aCanfosfamide and Topotecan I are two cohorts of the same trial comparing canfosfamide with PLD or topotecan. Patients were randomized to one of two treatment arms: canfosfamide or topotecan/PLD. Patients in the topotecan/PLD treatment arm chose one of the two treatments.

showed no significant difference in OS between C+PLD and C+P (HR, 0.95; 95% CI, 0.84–1.07; $p = .36$) (Fig. 3).

Grade 3–4 toxicities were evaluated provided they were reported in all three trials (Fig. 4). Meta-analysis showed that C+PLD was associated with a decreased risk of an allergic reaction (RR, 0.43; 95% CI, 0.26–0.71; $p = .001$) and neutropenia (RR, 0.84; 95% CI, 0.76–0.93; $p = .001$) compared with C+P. There was no difference in risk of infection between the two regimens (RR, 0.89; 95% CI, 0.45–1.75; $p = .73$). C+PLD was associated with an increased risk of anemia (RR, 1.96; 95% CI, 1.37–2.79; $p < .001$) and thrombocytopenia (RR, 3.44; 95% CI, 2.45–4.84; $p < .001$), which are other indices of myelosuppression in conjunction with neutropenia.

Grade 2 or higher toxicities were also evaluated (Fig. 4). C+PLD was associated with a decreased risk of allergic reactions (RR, 0.39; 95% CI, 0.27–0.55; $p < .001$; data not shown), alopecia (RR, 0.33; 95% CI, 0.298–0.372; $p < .001$), and neuropathy (RR, 0.18; 95% CI, 0.14–0.25; $p < .001$) compared with C+P. C+PLD was associated with an increased risk of mucositis/stomatitis (RR, 2.48; 95% CI, 1.76–3.51; $p < .001$), gastrointestinal [GI] toxicity (RR, 1.16; 95% CI, 1.09–1.23; $p < .001$), and cutaneous toxicity (RR, 5.6; 95% CI, 3.43–8.81; $p < .001$).

Monotherapy Regimens

The meta-analysis showed no difference in PFS (HR, 0.99; 95% CI, 0.89–1.11; $p = .93$) or OS (HR, 0.99; 95% CI, 0.88–1.11; $p = .86$) between single-agent PLD and other monotherapy regimens (Fig. 3).

PLD was associated with a decreased risk of neutropenia (RR, 2.37; 95% CI, 1.90–2.95; $p < .001$), anemia (RR, 1.85; 95% CI, 1.34–2.54; $p < .001$), thrombocytopenia (RR, 3.52; 95% CI, 2.02–6.16; $p < .001$), and GI toxicity (RR, 1.81; 95% CI, 1.53–2.14; $p < .001$) compared with the comparator regimens (Fig. 5). PLD was also associated with an increased risk of mucositis/stomatitis (RR, 0.10; 95% CI, 0.04–0.26; $p < .001$) compared with the other monotherapies (Fig. 5). There was no difference in risk of fatigue between the comparator regimens and PLD (RR, 1.22; 95% CI, 0.87–1.71; $p = .25$) (Fig. 5). Hand-foot syndrome was also evaluated in each trial with the exception of the trial containing the Topotecan II cohort. The incidence

of hand-foot syndrome in PLD-treated groups ranged from 5.5% to 37.5%. There were no cases of hand-foot syndrome in any comparator therapies.

Publication Bias

Publication bias was evaluated by funnel plot analysis of efficacy and toxicity data for both the doublet regimens and the monotherapy regimens (supplemental online Fig. 1). No evidence of publication bias was found in the trials included in the meta-analysis.

DISCUSSION

C+PLD

The results of our analysis showed that the combination regimen of C+PLD was associated with improved PFS compared with C+P in platinum-sensitive ovarian cancer. These results suggest that the combination may have better antitumor efficacy, perhaps by better targeting the tumor cells, thereby resulting in better on-treatment efficacy. PFS is not a surrogate marker for OS; however, PFS often mirrors OS data [8]. Our meta-analysis showed no difference in OS between the two regimens. Interpretation of PFS and OS results can be difficult, especially across different clinical studies. The factors that may affect these endpoints are numerous and have been discussed comprehensively in the literature [22, 23].

One possibility that has not been well studied is a biological explanation for the incongruity between PFS and OS results [24, 25]. This possibility is important to consider because it is not known whether PLD in the first-line setting may lead to drug resistance in the second-line setting, which would preclude the use of C+PLD again or C+P. It is possible that tumor cells that survive treatment with C+PLD may be more aggressive or may be resistant to subsequent therapies. Although this regimen has better on-treatment efficacy, when the disease does recur, it may progress more quickly or may be resistant to other therapies, thus negating any benefits for OS.

It has been reported that C+PLD may be associated with higher rates of mucositis/stomatitis, GI toxicity, cutaneous toxicity, and myelosuppression compared with C+P. The results of our meta-analysis confirm that C+PLD is associated

Efficacy of Doublet Regimens

A Progression Free Survival

B Overall Survival

Efficacy of Monotherapy Regimens

C Progression Free Survival

D Overall Survival

Figure 3. Forest plots of efficacy endpoints. **(A):** Progression-free survival (PFS) of doublet regimens. **(B):** Overall survival of doublet regimens. **(C):** PFS of monotherapy regimens. **(D):** Overall survival of monotherapy regimens. References: CALYPSO [19], MITO-2 [9], Hellenic [10], Gemcitabine I [16], Gemcitabine II [21], Topotecan II [13], Patupilone [15].

^aHazard ratios were extracted manually from Kaplan-Meier curves.

^bTime to progression was used because PFS was not reported.

Abbreviations: CI, confidence interval; PLD, pegylated liposomal doxorubicin.

Toxicity of Doublet Regimens

A Allergic Reaction (Grades 3–4) **B** Neutropenia (Grades 3–4) **C** Infection (Grades 3–4) **D** Anemia (Grades 3–4) **E** Thrombocytopenia (Grades 3–4) **F** Alopecia (All Grades) **G** Neuropathy (Grade 2 or Higher) **H** Mucositis/Stomatitis (Grade 2 or Higher) **I** GI Toxicity (Grade 2 or Higher) **J** Skin/Hand-Foot Syndrome (Grade 2 or Higher)

Figure 4. Forest plots of toxicity endpoints for the doublet regimens. (A): Allergic reaction. (B): Neutropenia. (C): Infection. (D): Anemia. (E): Thrombocytopenia. (F): Alopecia. (G): Neuropathy. (H): Mucositis/stomatitis. (I): Gastrointestinal toxicity. (J): Skin/hand-foot syndrome. References: CALYPSO [19], MITO-2 [9], Hellenic [10].

Abbreviations: CI, confidence interval; GI, gastrointestinal; PLD, pegylated liposomal doxorubicin.

with increased risk of mucositis/stomatitis, GI toxicity, and cutaneous toxicity; however, not all indices of myelosuppression were found to be increased with the C+PLD regimen. Although there was an increased risk of anemia and thrombocytopenia with C+PLD, there was also a decreased risk of neutropenia compared with C+P. The clinical advantage of this lower risk of neutropenia is unclear. On the one hand, despite a decreased risk of neutropenia, there was no difference in rates of infection between the two regimens. Furthermore, there was no difference in rates of febrile neutropenia reported in the CALYPSO and MITO-2 trials. On the other hand, anemia can lead to fatigue, which could significantly affect QOL; however, no differences in rates of fatigue were reported in CALYPSO or MITO-2. Finally, the increased risk of thrombocytopenia associated with C+PLD could result in increased risk of hemorrhage. The results from CALYPSO and MITO-2 showed a trend toward this because both studies reported grade 3–4 bleeding events in the C+PLD cohort (three cases and one case, respectively), whereas there

were no cases in the C+P group. The clinical impact of these events is unclear because these cases were rare and the difference was not statistically significant between the two treatment arms.

The results of our analysis also showed that C+PLD is associated with a decreased risk of allergic reactions compared with C+P. All three agents—carboplatin, PLD, and paclitaxel—are associated with allergic reactions that can lead to discontinuation of therapy. Unlike carboplatin hypersensitivity, which is a true allergic reaction, PLD and paclitaxel infusion reactions may be related to activation of the immune system by the liposomal carrier and the polyethoxylated castor oil (Cremophor EL) excipient, respectively [26, 27]. The reported rates of infusion reactions are similar with both agents, about 10%, and can be prevented effectively with prophylactic agents [28, 29]. The lower rates of allergic reactions in the C+PLD regimen suggest that there may be an unknown mechanism by which PLD decreases carboplatin hypersensitivity. This could be of high clinical importance because allergic reac-

Toxicity of Monotherapy Regimens

A Neutropenia

B Anemia

C Thrombocytopenia

D GI Toxicity

E Mucositis/Stomatitis

F Fatigue

Figure 5. Forest plots of toxicity endpoints (grades 3–4) for monotherapy regimens. (A): Neutropenia. (B): Anemia. (C): Thrombocytopenia. (D): Gastrointestinal toxicity. (E): Mucositis/stomatitis. (F): Fatigue. References: Gemcitabine I [16], Gemcitabine II [21], Topotecan I [22], Topotecan II [13], Canfosfamide [22], Patupilone [15].

Abbreviations: CI, confidence interval; GI, gastrointestinal; PLD, pegylated liposomal doxorubicin.

tions to platinum agents can affect up to 12% of patients [30] and can lead to discontinuation of platinum therapy.

We found that neuropathy and alopecia were also lower with the C+PLD regimen compared with C+P. This is consistent with the results reported in individual clinical trials. Although not necessarily life threatening, neuropathy can be dose limiting and functionally debilitating [31], and alopecia can have a significant impact on a patient's psychological well-being [32, 33]. These side effects are important to consider when choosing therapeutic strategies.

We do not see convincing evidence that C+PLD is more tolerable than C+P. Rather, we find that the toxicity profiles are simply different between the two regimens. Our conclusion is supported by the findings of MITO-2 and CALYPSO, which showed no significant difference in health-related QOL between the two regimens after three or six cycles of treatment [9, 11]. The unique toxicity profile of C+PLD may be beneficial for patients who want to avoid neutropenia, neuropathy, or alopecia; however, there may be a decrease in QOL from GI toxicity, anemia, thrombocytopenia, cutaneous toxicity, and mucositis/stomatitis.

Another potential role for PLD in the initial treatment of ovarian cancer is as an add-on agent to a C+P regimen. This regimen was evaluated in GOG182-ICON5 [34], a multicenter, randomized, phase III clinical trial with five treatment arms, that enrolled 4,312 ovarian cancer patients. This landmark trial, using eight cycles of C+P as the reference arm, evaluated four other regimens: eight cycles of C+P with PLD every other cycle, eight cycles of C+P and gemcitabine, four cycles of carboplatin with topotecan followed by four cycles of C+P, or four cycles of carboplatin with gemcitabine followed by four cycles of C+P. The results of this trial showed no difference in PFS or OS between C+P and any of the other regimens. This suggests that there is no benefit to adding PLD or another cytotoxic agent to C+P. Our findings also corroborate the findings of this study, showing that there may be similar efficacy across different platinum-based doublet regimens.

Single-Agent PLD

Unlike the patients in the C+PLD regimens, the patients in the monotherapy regimens had more advanced disease, were heavily pretreated, and usually were platinum resistant. The trial containing the Topotecan II cohort was the only one to report a difference in survival, favoring the PLD regimen (OS: HR, 1.23; 95% CI, 1.009–1.499; $p = .040$). This was different from the results of the other comparator regimens (gemcitabine and patupilone) and of our overall meta-analysis, which showed no difference in PFS or OS between PLD and other regimens. Using the Response Evaluation Criteria in Solid Tumors, objective response rates were typically less than 30% for the monotherapies evaluated. These low response rates, coupled with the results of our analysis, suggest that these single-agent treatments generally have low efficacy in this setting. Recently, there have been trials evaluating the efficacy of novel treatment combinations such as trabectedin with PLD and canfosfamide with PLD compared with single-agent PLD in recurrent or platinum-resistant ovarian cancer [9, 10]. In addition, a novel targeted agent, olaparib (a poly[ADP-ribose] polymerase inhibitor), was compared with single-agent PLD in *BRCA1*- or *BRCA2*-positive recurrent ovarian cancer patients [35]. These trials have not shown improvements in PFS or OS, although there was a trend toward additional toxic-

ity [9, 10, 35]. It is imperative that new treatments are identified for this patient population.

The results of our analysis showed that PLD monotherapy is associated with an increased risk of cutaneous toxicity and mucositis/stomatitis; however, PLD was associated with decreased risk of GI toxicity and myelosuppression (anemia, neutropenia, and thrombocytopenia). Yet, there were no differences in the risk of fatigue. Of note, patupilone was the only treatment associated with a decreased risk of neutropenia compared with the PLD group; this finding differed from all other cohorts and from the overall results of our meta-analysis. Our findings support that PLD is more tolerable than the other agents because there is less anemia, neutropenia, thrombocytopenia, and GI toxicity, but some major differences in side effect profiles of the comparator regimens, such as patupilone, warrant further evaluation. The results of our meta-analysis suggest that there is similar efficacy among PLD, gemcitabine, topotecan, and patupilone. PLD appears to be more tolerable, which may enable patients to have a better QOL. This is an important distinction because, in this setting, monotherapy is considered more palliative, and concerns for QOL become paramount.

Other Considerations

A drawback of our study was the limited nature of our meta-analysis. A relatively low number of trials met the criteria for inclusion in this study. This raises the question of potential error from publication bias; however, funnel plot analyses did not reveal any publication bias. Nonetheless, our results should be interpreted with caution, especially because these were all open-label studies. This approach could unwittingly result in premature treatment discontinuation if patients were dissatisfied with treatment allocation.

It is important to consider that when ovarian cancer recurs after initial treatment with C + P, some patients can still benefit from second-line therapy with C + P again or with C + PLD. It is not known whether the same scenario would hold true for patients who were initially treated with C + PLD. Will PLD in the first-line setting lead to drug resistance in the second-line set-

ting, which would preclude the use of C + PLD again or of C + P? It is also not known how first- or second-line therapy with C + PLD would affect the progression of ovarian cancer and responses to other therapies. There is an urgent need for further studies to fully elucidate the role of the doublet regimen of C + PLD and single-agent PLD in ovarian cancer.

CONCLUSION

The findings of our analysis support C + PLD as a possible alternative to C + P for ovarian cancer, with similar efficacy in both regimens. Because the side effect profiles of the two regimens are drastically different, the choice of regimen could reasonably be based on individual patient preference to avoid certain side effects. In the recurrent or refractory setting where platinum resistance is likely to exist, there is similar efficacy among the monotherapy agents, but PLD may be more tolerable. The overall low response rates in this population highlight an imperative need to identify more efficacious treatments. In addition, further studies are needed to determine the impact of first- or second-line C + PLD therapy on development of drug resistance and responses to subsequent therapies when the disease recurs.

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DISCLOSURES

The authors indicated no financial relationships.

Section editors: Dennis Chi: None; Peter Harper: Sanofi, Roche, Imclone, Pfizer, GlaxoSmithKline, Lilly, Genentech (C/A); Lilly, Novartis, Sanofi, Roche (H)

Reviewer "A": None

Reviewer "B": None

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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