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Necessity of routine cardiac evaluation in patients receiving pegylated liposomal doxorubicin for gynecologic cancer

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HIGHLIGHTS

- In our cohort, there was no difference in median ejection fraction before and after treatment with PLD.
- Cumulative exposure to PLD was not associated with cardiotoxicity when excluding women who received <1800 mg.
- Individualized, rather than routine, cardiac evaluation in women receiving PLD may be appropriate.

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ABSTRACT

Objective: Pegylated liposomal doxorubicin (PLD) has similar reported clinical efficacy compared with conventional doxorubicin with less cardiotoxicity. The manufacturer of PLD advises that cardiac function should be evaluated with endomyocardial biopsy, echocardiography or multigated radionucleotide scan (MUGA) pre-treatment and during therapy. This study was designed to assess the necessity of pre-treatment cardiac evaluation in patients receiving PLD.

Methods: After IRB approval, a retrospective study of all women with gynecologic cancer who received PLD from 2006 to 2018 was performed. Demographic information, treatment records, cardiac risk factors, and cardiac surveillance testing were examined. Wilcoxon signed rank sum test and logistic regression were used to evaluate the association of cumulative PLD exposure with cardiotoxicity.

Results: A total of 235 patients received PLD for gynecologic cancer. Patients received a median of 3 cycles of PLD with a cumulative dosage of 237 mg over a median follow-up time of 24 months. Sixteen patients in the cohort (7%) had no cardiac surveillance at all. Of the remaining patients who underwent cardiac testing, 183 (84%) received MUGA scans and 36 (16%) had echocardiography. Of the 56 patients who had both pre- and post-treatment cardiac testing, there was no significant difference in median ejection fraction ($p = 0.17$). Three patients developed PLD-associated cardiac toxicity but only one patient had severe manifestations requiring discontinuation of PLD therapy.

Conclusions: Routine cardiac testing before, during or after treatment with PLD may be unnecessary. Cardiac testing may be more appropriate for individual patients for whom the clinical suspicion of PLD-related cardiac toxicity is high.

1. Background

Pegylated liposomal doxorubicin (PLD) is an anthracycline topoisomerase inhibitor commonly used as a chemotherapeutic agent in the treatment of a variety of solid malignancies, including recurrent or progressive gynecologic cancer [1]. The liposomal formulation of doxorubicin contains a polyethylene glycol layer surrounding the doxorubicin, protecting it from being phagocytosed and therefore prolonging its half-life [2]. The biodistribution of the PLD form is such that it accumulates in the liver, spleen and tumor and is not deposited in the cardiac tissue [3]. This formulation was demonstrated in animal models to decrease the cardiotoxicity of PLD as compared to doxorubicin (16% vs 67%) [4]. The biodistribution of PLD allows for more directed therapy compared with the greater restriction of the non-pegylated agent due to its cardiotoxic effects [5]. Several studies have affirmed PLD's use as an

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effective alternative to conventional doxorubicin given its relatively favorable cardiotoxicity and side effect profile [6–8].

It is well documented that anthracycline treatment is associated with an increased risk of cardiotoxicity and it appears to be dependent on cumulative dose and schedule. In a clinical study of patients with advanced breast cancer who received a cumulative dose of between 450 and 550 mg of PLD, the risk of cardiac toxicity was 11% [11]. However, it is important to note that given the time frame of this study a number of the patients had probably already been exposed to doxorubicin and were already at risk for cardiotoxicity. High cumulative doses of PLD above the Federal Drug Administration's initial recommended lifetime total cumulative dose of 550 mg are often seen in the treatment of ovarian cancer. Several studies have examined the utility of cardiac function surveillance in patients receiving PLD as part of a chemotherapeutic regimen, however the evidence supporting the guidelines dictating standard practice in these patients are lacking [7–10].

Routine assessment of left ventricular ejection fraction (LVEF), either by multigated radionuclide angiography (MUGA) or echocardiography, is recommended by the Food and Drug Administration (FDA) prior to, during and after treatment with PLD. The drug insert for PLD states “cardiac function should be carefully monitored in patients treated with [PLD]. Echocardiography or multigated radionuclide scans, have been used to monitor cardiac function and these methods should be employed to monitor potential cardiac toxicity.” () The objective of our study is to evaluate the association of cumulative dosage of PLD with incident cardiac toxicity in a cohort of women receiving PLD for gynecologic cancers.

2. Methods

After approval by our Institutional Review Board, a retrospective cohort study was performed that included all women who received PLD as part of a chemotherapy regimen for the treatment of gynecologic malignancy between January 2006 and January 2018 at a single institution. Clinical data was abstracted from the medical records including patient age, race, cancer stage, pathology, body mass index (BMI) at time of chemotherapy and chart-indicated diagnosis of co-morbidities that have classically been associated with cardiac disease: hypertension, hyperlipidemia, venous thromboembolism, coronary artery disease, myocardial infarction, diabetes, smoking status and obesity. Treatment data including the number of prior chemotherapy regimens, the total number of cycles of PLD and the cumulative dose of PLD was calculated.

Cardiac ejection fraction obtained from MUGA scan or echocardiography was recorded and characterized according to when the test was obtained in relation to the PLD administration: before, during or after the chemotherapy. For patients who had both baseline and post-treatment cardiac function data available, equality of matched ejection fractions was assessed using the Wilcoxon signed rank sum test. Univariate logistic regression was performed to assess the association of individual variables with PLD- related congestive heart failure. Odds ratios were reported with 95% confidence intervals. Cardiac toxicity during treatment was defined as acute coronary syndrome, CHF or signs of cardiac dysfunction on ECHO or MUGA scan, including a drop in LVEF below 50%, or a 10% decrease in LVEF from baseline. Statistical analysis was performed using Stata version 14.2 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). A p value of <0.05 was considered significant.

3. Results

Two hundred and thirty-five patients with gynecologic cancer were identified who received PLD during the specified time period.

Table 1
Demographic and clinicopathologic data for patients who received pegylated liposomal doxorubicin for gynecologic malignancy ($N = 235$)[a].

Characteristics	N (%)
Age (years)	62 ± 11
Race	
White	65 (28)
Black	86 (37)
Hispanic	73 (31)
Asian	7 (3)
Other/Unknown	4 (2)
Primary disease site	
Uterus	117 (50)
Ovary	86 (37)
Fallopian tube	11 (5)
Primary peritoneal	18 (8)
Cervical	3 (1)
Histology	
Serous	151 (64)
Endometrioid	42 (18)
Clear cell	12 (5)
Carcinosarcoma	13 (6)
Leiomyosarcoma	8 (3)
Other	9 (4)
Cancer stage	
Stage I	28 (12)
Stage II	7 (3)
Stage III	94 (40)
Stage IV	106 (45)
Grade of tumor	
Grade 1	9 (4)
Grade 2	10 (4)
Grade 3	216 (92)
Medical comorbidities	
Hypertension	142 (60)
Hyperlipidemia	58 (25)
Venous thromboembolism	33 (14)
Coronary artery disease	5 (2)
Myocardial infarction	3 (1)
Diabetes	54 (23)
Current smoker	21 (9)
Obesity	93 (40)
Body mass index (kg/m^2)	29.0 ± 7.1

[a] Data with plus-minus values represent means ± standard deviation, otherwise categorical data are presented as N (%).

Median follow-up time for the cohort was 24 months. The demographic, clinical and pathologic data for patients who received PLD are summarized in Table 1. The mean age at initiation of PLD therapy was 62 years ±11 years. The primary origin of the cancer being treated was ovarian, fallopian tube or primary peritoneal

Table 2
Treatment data for patients with gynecologic cancer who received pegylated liposomal doxorubicin (PLD) (N = 235).

Characteristics	N (%)
Number of prior chemotherapy regimens	1 (1, 1)
Cycles of PLD administered	3 (2, 6)
Cumulative dosage of PLD (mg)	237 (150, 373)
Cardiac testing modality[a]	
MUGA	183 (84)
Echocardiogram	36 (16)
Timing of cardiac testing	
No testing	16 (7)
Prior to chemotherapy	151 (64)
During chemotherapy	1 (0.4)
After chemotherapy	4 (2)
Prior to and during chemotherapy	7 (3)
Prior to and after chemotherapy	49 (21)
Prior to, during and after chemotherapy	7 (3)
Developed PLD-related cardiotoxicity	3 (1)

Data represent medians (interquartile range), otherwise categorical data are presented as N (%).
[a] Based on the 219 patients who received cardiac testing.

carcinoma in 118 (50%) patients and endometrial carcinoma in 117 (50%) patients. The median cumulative dose of administered PLD was 237 mg (IQR 150–373 mg) with a median of 3 cycles per patient (IQR 2–6 cycles) (Table 2). Seventeen women (7%) received cumulative dosages of PLD exceeding 550 mg. The data were assessed for temporal trends in cumulative dosage of PLD over the study period and no significant trends were found ($p = 0.93$).

The mean pre-treatment ejection fraction for the cohort was 63.8 ± 6.7%. For the 56 women who had both pre- and post- treatment cardiac testing data available, there was no significant difference in the median ejection fraction ($p = 0.17$). In simple logistic regression, cumulative PLD dosage was significantly associated with cardiotoxicity with each 10 mg of PLD conferring an additional 4% odds of cardiotoxicity (OR 1.04; 95% CI 1.01–1.07) (Table 3). Likewise, each additional cycle of PLD was associated with a 32% increased odds of developing cardiotoxicity (OR 1.32, 95% CI 1.07–1.64). However, when excluding the one patient who had a cumulative dosage of 1898 mg, this association became insignificant (OR 0.99; 95% CI 0.89–1.09). No additional covariates were significantly associated with cardiac toxicity in the logistic regression.

Three patients in the cohort developed cardiac toxicity during treatment with PLD (Table 4). The first patient was a fifty-year-old with no cardiac risk factors who received 330 mg PLD. While undergoing routine cardiac screening for a separate phase I study she was found to have a drop in her ejection fraction from 80% to 63% which was attributed by her cardiologist to her prior PLD exposure. The second patient was a sixty-nine-year-old with a history of a prior venous thromboembolism who received 1898 mg of PLD. She presented with dyspnea and chest pain and was found to have a decrease in her ejection fraction from 50% to 40%. The third patient was a seventy-three-year-old with a history of hypertension and hyperlipidemia who received 144 mg of PLD. She presented with dyspnea and was found to have a decrease in ejection fraction from 60% to 25%. Two of these patients had significant clinical manifestations prompting repeat cardiac function testing: one patient developed symptoms five weeks after completing PLD therapy and the other developed symptoms three months after PLD completion. It is important to note that the patient who experienced clinical manifestations five weeks after PLD therapy received 1898 mg of PLD and was the only patient who developed cardiac toxicity within the cohort of patients that received >550 mg of PLD. This is the only patient in the cohort whose PLD was discontinued due to cardiac toxicity and she remains alive 28 months after discontinuation of the PLD therapy. Her repeat post-treatment ejection fraction subsequently recovered to her baseline. The third patient with cardiac toxicity in the absence of clinical manifestations was noted to have an incidentally decreased, yet still normal, ejection fraction on repeat cardiac function prior to starting a separate phase I study.

4. Discussion

Our data suggests that women receiving PLD for gynecologic malignancy have a very low incidence of PLD-related cardiac toxicity. Regardless of cardiac surveillance, 99% of patients did not develop cardiac dysfunction and none of the patients who developed cardiac toxicity experienced severe morbidity or mortality. Of the three patients that developed cardiac toxicity, only one patient had severe symptoms requiring discontinuation of the PLD therapy. Additionally, the cumulative dose was not significantly associated with cardiotoxicity when excluding the patient who received an additional 1000 mg of PLD greater than anyone else in the cohort. Our study suggests that it may be reasonable to omit cardiac surveillance in asymptomatic patients receiving PLD for gynecologic cancers.

Previous studies have examined algorithms for cardiac surveillance during PLD treatment, including baseline cardiac imaging and additional imaging if at higher risk of developing cardiac toxicity [1,6,7,12]. Higher risk patients included those with ejection fractions of 30–50%, previous irradiation to the chest or anthracycline exposure and total treatment of >250 mg/m^2 of doxorubicin. This algorithm decreased doxorubicin associated cardiac toxicity to 3% [13]. Additional retrospective studies have also looked at PLD associated cardiac toxicity [1,6,7]. The largest of these studies included a cohort of 141 patients and noted only one clinically significant decrease in ejection fraction. Interestingly, this patient had a total dose of 1670 mg/m^2, similar to the one patient in our study who had a clinically significant decrease in cardiac function [1]. Studies in patients with non-gynecologic malignancies have also demonstrated similar conclusions [14]. Additional studies have also suggested a significant cost saving for selectively performing cardiac surveillance only in patients with a cardiac history or symptoms suggestive of cardiac toxicity [15].

The strengths of our study include the relatively large sample size and the long follow up of these patients. The weaknesses of this study include its' retrospective nature and the inability to infer causality or details about the true incidence of cardiotoxicity in this population without a prospective design. Given the very few cardiotoxicity events that actually occurred, it is difficult to draw definitive conclusions based on the limited number of adverse cardiac events. Furthermore, not all of our patients had both pre- and post- treatment ejection fractions available for analysis which further limited the analysis and conclusions. Finally, in 2012 the American Society of Clinical Oncology (ASCO) revised guidelines for dosing of obese patients. While theoretically, under-dosing of obese patients prior to 2012 could account for the low rate of cardiotoxicity observed in our cohort, we did not observe any temporal differences in either cumulative PLD dosage ($p = 0.93$) or obesity ($p = 0.87$) during the follow-up period.

Our data supports the prior literature suggesting that routine cardiac surveillance may not be necessary in women with gynecologic cancer receiving PLD chemotherapy. Although our study was not designed to test this hypothesis, there may be a place for cardiac surveillance in patients with increased baseline risk of cardiotoxicity or known cardiac dysfunction prior to initiating treatment. There may also be a place for interval cardiac surveillance in patients receiving a life-time cumulative dose considerably greater than the 550 mg/m^2 recommended by the FDA.

Table 3
Logistic regression examining association of cumulative exposure to pegylated liposomal doxorubicin (PLD) with cardiotoxicity (N = 235).

	OR[b]	95% CI	*P*-value
Cumulative dosage of PLD (10 mg increments)	1.04	1.01–1.07	<0.01
Cumulative dosage of PLD (10 mg increments) excluding outlier[a]	0.99	0.89–1.09	0.77
Number of Cycles of PLD	1.32	1.07–1.64	<0.01
Number of Cycles of PLD excluding outlier	0.92	0.46–1.84	0.81

[a] Outlier refers to a single patient with a cumulative lifetime PLD exposure of 1898 mg.
[b] OR refers to the odds of developing cardiotoxicity with each additional 10 mg or each additional cycle of PLD administered.

5. Conclusion

Cardiac toxicity with PLD therapy in women with gynecologic cancer is rare. We suggest that routine cardiac surveillance for patients receiving PLD treatment may not be necessary. Further prospective studies are needed to change recommendations for pre- and post-treatment cardiac testing, as some providers have already transitioned to individualized testing based on risk-factors for PLD-associated cardiotoxicity.

Table 4
Clinicopathologic data of patients in the cohort who developed PLD-related cardiotoxicity ($N = 3$).

Age	Cumulative dose (mg)	Risk factors	Pre-treatment Ejection Fraction (%)	Repeat Post-Treatment Ejection Fraction (%)	Repeat ECHO/MUGA Indication	Timing of Repeat ECHO/MUGA
50	330	None	80	63	Routine screening prior to phase I study	10 months after PLD
69	1898	Prior VTE	50	40	Dyspnea and chest pain	5 weeks after PLD
73	144	HTN, HLD	60	25	Dyspnea	3 months after PLD

Author contributions

Dr. Dioun is the first author on the manuscript. He performed the data collection and was principally involved in the preparation of the manuscript.

Dr. Vilardo and Dr. Goldberg served as co-authors on the manuscript and made substantial contributions and revisions to the final draft.

Dr. Gressel is the lead author on the manuscript and was involved in the supervision of the design, data collection, analysis and preparation of the manuscript.

Declaration of competing interest

The authors of this manuscript have no relevant conflicts of interest to report.

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