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Incidence of Cardiotoxicity Associated with the Use of Pegylated Liposomal Doxorubicin in Gynecologic Malignancies

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ABSTRACT

OBJECTIVE This study aims to evaluate the incidence of cardiotoxicity in patients with gynecologic cancer undergoing pegylated liposomal doxorubicin (PLD) treatment and to identify risk factors for developing changes in the left ventricular ejection fraction (LVEF).

METHODS A retrospective analysis was conducted on patients with gynecologic malignancies who had received PLD treatment at Phramongkutklao Hospital from January 2013 through December 2022. Cardiotoxicity was defined as a confirmed diagnosis of congestive heart failure or a decline in LVEF of 10% or more. Spearman's correlation and mixed modeling were used to analyze the relationship between patient factors and MUGA variations.

RESULTS A total of 34 patients were included in the study. The median number of PLD cycles was six, with a median cumulative dose of 240 mg. No patient experienced doxorubicin-induced cardiotoxicity. Among the 19 patients with available pre- and post-treatment LVEF measurements, no significant decline in LVEF was observed following PLD (MD 6.6%, p = 0.124). However, Spearman's correlation analysis revealed a negative correlation between high cumulative PLD doses (exceeding 1,500 mg) and LVEF change (coefficient = -0.53, $p < 0.001$). Mixed model analysis suggested a potential association between higher body mass index (BMI) and decreased LVEF post-treatment (β = -1.21, p = 0.036), while diabetes may be associated with improved LVEF outcomes (β = 12.18, p = 0.033).

CONCLUSIONS There were no cases of cardiotoxicity after PLD treatment. A potential association between higher BMI and decreased LVEF was found. A high cumulative PLD dose is correlated negatively with LVEF change. Cardiac monitoring is recommended for selected patients, particularly those who are obese or have received cumulative PLD doses exceeding 1,500 mg.

KEYWORDS pegylated liposomal doxorubicin, anthracycline, gynecologic cancer, cardiotoxicity

INTRODUCTION

Pegylated liposomal doxorubicin (PLD) is one of the mainstay chemotherapy treatments for advanced or recurrent gynecologic cancer because of its efficacy and tolerable toxicity (1, 2). PLD has been previously shown to have a safer cardiac toxicity profile compared with doxorubicin (3, 4). However, due to the lack of consistent standards

and recommendations, anthracycline-induced heart failure remains a source of concern and confusion in some aspects of cardiotoxicity monitoring. Cardiac function evaluation before PLD treatment can include multiple-gated acquisition (MUGA) or echocardiography (5). Subsequently, repeat testing may be performed at the physician's discretion. Several studies have demonstrated that gynecological cancer patients who received PLD did not develop heart failure or a decrease in left ventricular ejection fraction (LVEF) (6, 7). However, patients who received a high PLD dose and individuals with preexisting cardiovascular disease experienced doxorubicin-induced cardiotoxicity (8). Therefore, the necessity for and cost-effectiveness of LVEF monitoring in this patient population remains unclear.

The present study was conducted to investigate the incidence of anthracycline-induced cardiotoxicity among PLD-treated gynecologic cancer patients with the aim of establishing associations between LVEF changes and the cumulative dose of PLD, as well as correlations between LVEF changes and presumed risk factors.

METHODS

A retrospective study was conducted at Phramongkutklao Hospital in Bangkok, Thailand, between January 1, 2013 and December 31, 2022. The study protocol was approved by the hospital Institutional Review Board. The study cohort consists of gynecologic cancer patients who had undergone chemotherapy with PLD. Patients who received conventional doxorubicin treatment and those with incomplete medical records were excluded. A previous study reported a cardiotoxicity rate of 3 out of 235 cases in patients who were administered PLD (9). Based on that information, a sample size of 17 was determined, with a margin of error of 0.05. Clinical data were obtained from medical records and included demographic information such as age, height, and weight, as well as co-morbidities such as hypertension, diabetes mellitus, and dyslipidemia. Additionally, information on pre-existing cardiovascular diseases such as cerebrovascular accidents, venous thromboembolism, chronic kidney disease, and myocardial and pericardial disorders was collected.

Information was acquired on the types, grades, and International Federation of Gynecology and Obstetrics staging of the gynecologic cancers. For PLD, we focused on the number of cycles, the mean dosage per cycle, and the cumulative dose. We obtained LVEF data from a MUGA scan or echocardiography as a percentage before therapy as well as a subsequent value after PLD use. Doxorubicin-induced cardiotoxicity can manifest in two situations: 1) in patients diagnosed with congestive heart failure during PLD treatment, and 2) in asymptomatic patients whose LVEF decreased by over 10% from baseline (5).

Statistical analyses were conducted using STATA version 17. Descriptive statistics are reported as frequency (percentage), mean ± standard deviation, and median (interquartile range). Spearman's correlation was used to measure the correlation between patient factors and MUGA variations. The mixed model was used to conduct univariate and multivariate analyses due to the small sample size and the non-normal data distribution. A p-value < 0.05 was considered statistically significant.

RESULTS

The study identified 38 gynecologic cancer patients treated with PLD between 2013 and 2022. From that number, three patients who had received conventional doxorubicin and one patient with missing LVEF data were excluded, giving a study population of 34 patients. The baseline characteristics of the included patients are described in Table 1. Fourteen patients had primary disease, while 20 had recurrent disease. A total of 24 ovarian cancer cases, 6 endometrial cancer cases, 3 peritoneal cancer cases, and 1 fallopian tube cancer case had previously been identified. The average age of the patients was 58 years and the average body mass index (BMI) was 23.75 kg/m^2. Pre-existing medical conditions included cardiovascular disease (5 cases), hypertension (12 cases), dyslipidemia (11 cases), and diabetes (5 cases). The majority (82%) had received a PLD dose of 40 mg/m^2. The median cumulative PLD dose was 240 mg (IQR: 140–360 mg). The median number of cycles per patient was six (IQR: 3–9 cycles). Pre-treatment LVEF averaged 61.78%. The first and second post-treatment measurements showed an average LVEF of 66% and 65%, respectively (Table 2).

Table 1. Patients' baseline characteristics data (N = 34)

Characteristics	N (%)
Age (years)	58.15±10.76
Height (cm)	155.88±5.85
Weight (kg)	57.5±12.31
BMI (kg/m^2)	23.75±5.34
Type of cancer	
Endometrium	6 (17.7)
Fallopian tube	1 (2.9)
Ovary	24 (70.6)
Peritoneum	3 (8.8)
Treatment type	
Primary disease	14 (41.2)
Recurrent disease	20 (58.8)
Underlying disease	
Hypertension	12 (35.3)
Dyslipidemia	11 (32.4)
Diabetes mellitus	5 (14.7)
Cardiovascular disease	5 (14.7)

Table 2. Treatment data of patients receiving pegylated liposomal doxorubicin (PLD) (N = 34)

Treatment data	N (%)
PLD dose	
40 mg/m^2	28 (82.4)
30 mg/m^2	6 (17.6)
Number of previous CMT regimens (cycles), median [IQR]	9 [6, 12]
Numbers of PLD given (cycles), median [IQR]	6 [3, 9]
Accumulated PLD dose (mg), median [IQR]	240 [140, 360]
Clinical CHF	0 (0.0)
%LVEF decreases > 10%	0 (0.0)
%LVEF from MUGA	
Pre-treatment LVEF (n=34)	61.78±12.55
1st follow-up LVEF (n=19)	66.11±8.97
2nd follow-up LVEF (n=12)	65.67±7.87

CHF, congestive heart failure; CMT, chemotherapy; MUGA, multiple-gated acquisition; LVEF, left ventricular ejection fraction

No patient developed congestive heart failure during PLD therapy. Nineteen patients underwent pre-treatment and the first follow-up LVEF assessment. Although a mean improvement of 6.6% in LVEF was observed following PLD treatment (pre-treatment: 59.5%, follow-up: 66.1%), this change was not statistically significant (p = 0.124).

Among the investigated factors associated with LVEF changes (Table 3 and Figure 1), PLD appears to have had no impact on LVEF when the total dosage used was below 660 mg. However, we observed a significant decrease in LVEF for patients who received a higher cumulative dose of between 1,560 mg and 1,680 mg (correlation coefficient = -0.53, $p < 0.001$). Both BMI and the number of PLD cycles were statistically significantly associated with a negative impact on LVEF, with correlation coefficients of -0.47 and -0.48, respectively. Hypertension and dyslipidemia also demonstrated negative correlations with LVEF, but those associations were not statistically significant. In contrast, patient age was positively associated with LVEF changes with a correlation coefficient of 0.35. Diabetes was also found to have a positive association with LVEF; however, the effect correlation was not statistically significant.

Table 3. Spearman's rank correlation of various risk factors and LVEF changes

Variables	LVEF change	
	r	p-value
Weight	-0.464	0.005
BMI	-0.470	0.004
Age	0.355	0.036
PLD dose	-0.270	0.117
Accumulated PLD dose	-0.530	0.001
Cycles of PLD given	-0.483	0.003
Hypertension	-0.037	0.832
Dyslipidemia	-0.149	0.393
Diabetes mellitus	0.310	0.070
Cardiovascular disease	0.165	0.342

BMI, body mass index; LVEF, left ventricular ejection fraction; PLD, pegylated liposomal doxorubicin

In univariate regression analysis, five variables were found to be statistically linked with LVEF changes: BMI, age, accumulated dose of PLD, cycles of PLD administration, and diabetes. The multivariate regression analysis showed that BMI is a significant predictor of negative changes in LVEF, with a β coefficient of -1.21 and a p-value of 0.036, while diabetes is statistically associated with increases in LVEF (β = 12.18, p = 0.033). The patient's age is also statistically associated with slightly positive changes in LVEF (β = 0.61, p = 0.035). Multivariate analysis showed that the cumulative dose and number of PLD cycles had no statistically significant effect on LVEF change (Table 4).

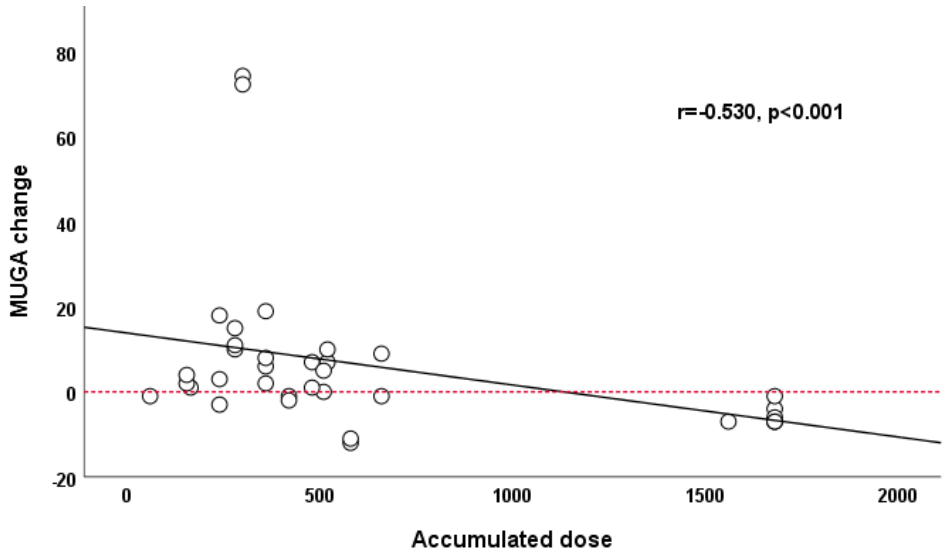

Figure 1. Correlation between accumulated PLD dose and LVEF changes

Table 4. Univariate and multivariate regression analysis by mixed model

Variables	Univariate				Multivariate			
	Beta coefficients	95%CI		*p*-value	Beta coefficients	95%CI		*p*-value
Weight	-0.70	-1.13	-0.26	0.002*				
BMI	-1.28	-2.33	-0.22	0.018*	-1.21	-2.35	-0.08	0.036*
Age	1.00	0.29	1.71	0.006*	0.61	0.04	1.17	0.035*
PLD dose	-0.02	-1.30	1.27	0.978				
Accumulated dose	-0.01	-0.02	0.00	0.022*	0.01	-0.05	0.06	0.775
Cycles of PLD given	-0.82	-1.59	-0.04	0.039*	-0.24	-3.94	3.47	0.900
Hypertension	5.26	-6.78	17.30	0.392				
Dyslipidemia	2.92	-9.20	15.05	0.637				
Diabetes mellitus	20.70	8.10	33.29	0.001*	12.18	0.97	23.38	0.033*
Cardiovascular disease	-0.57	-16.54	15.41	0.944				

PLD, pegylated liposomal doxorubicin

DISCUSSION

We observed around 50% of the cohort using MUGA scans for cardiac monitoring. There were no incidences of anthracycline-induced cardiotoxicity in the PLD-treated gynecologic patients. There were no significant differences between LVEF prior to and following PLD therapy (mean difference 6.6%, p = 0.124). None of the patients in the cohort presented with high-risk factors for cardiotoxicity, e.g., a history of chest wall/mediastinal radiotherapy or a previous diagnosis of congestive heart failure (10) which could explain the low incidence of anthracycline-induced cardiotoxicity in our group.

Cumulative PLD dosages below 660 mg showed no effect on LVEF variations. In contrast, a high cumulative PLD dose was correlated negatively with LVEF change. Previous studies have reported that LVEFs demonstrate a clinical reduction when exposed to cumulative doses exceeding 1,000 mg/m^2 (9, 11). Several previous studies have reported no significant association between high cumulative PLD doses (exceeding 1,000 mg/m^2) and cardiotoxicity (7). One study reported minimal LVEF changes in only 14% of patients within the high-dose group (3). In the present study, two of the thirty-four patients with PLD levels of 1,560 and 1,680 mg, respectively, did not develop clinical heart failure. While Spearman's analysis indicated a negative correlation between high PLD dose and LVEF change, this relationship did not show statistical significance in multivariate analysis. This discrepancy may be due to the small sample size, with only two cases exceeding 1,000 mg PLD doses.

Mixed model analysis indicates that obesity significantly reduces LVEF. A retrospective study investigating breast cancer patients treated with anthracyclines reported an association between obesity and cardiotoxicity (odds ratio [OR] 3.02; 95%CI 1.10–8.25; $p = 0.03$) (12). Surprisingly, diabetes seems to have a statistically significant beneficial effect on LVEF changes, although other cardiovascular risk factors, e.g., underlying cardiovascular disease, hypertension, and dyslipidemia, do not show a significant effect on the change in LVEF. However, as the present study had a limited sample size, further research with a larger number of participants is needed to confirm these findings.

A strength of the study is that a greater proportion of the patients had undergone cardiac monitoring which aided the effort to establish a correlation between LVEF changes and several potential risk factors. Limitations include a relatively small sample size. Lack of sufficient Data on the median follow-up duration was also a challenge in our study.

Our findings suggest that routine cardiac monitoring may not be necessary for most gynecologic cancer patients undergoing PLD. However, continuous cardiac monitoring should be considered for high-risk patients (8), such as those who are obese or have received cumulative PLD doses exceeding 1,500 mg.

CONCLUSIONS

There were no cases of cardiotoxicity after PLD treatment. A potential association between higher BMI and decreased LVEF was found. A high cumulative PLD dose is correlated negatively with LVEF change. Cardiac monitoring should be considered in selected patients.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author contributions

T.A.: Data curation, writing- original draft preparation; S.P.: conceptualization, methodology, writing – review & editing; K.R.: review & editing; S.I.: supervision, review & editing.

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