Gynecologic Oncology Reports 58 (2025) 101727

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Pegylated liposomal doxorubicin does not affect cardiac function in patients treated for gynecologic malignancies

Khrystyna Levytska [a,*], R. Wendel Naumann [b], Miranda J. Benfield [b], Jubilee Brown [b], Yovanni Casablanca [b], Brittany Lees [b], Allison M. Puechl [b], Erin K. Crane [b]

[a] Division of Gynecologic Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA
[b] Division of Gynecologic Oncology, Levine Cancer Institute, Atrium Health, Charlotte, NC, USA

ARTICLE INFO

Keywords:
Gynecologic malignancy
Pegylated liposomal doxorubicin
Cardiotoxicity
Left ventricular ejection fraction
Echocardiogram

ABSTRACT

Objective: Although pegylated liposomal doxorubicin (PLD) has a more favorable side-effect profile compared to doxorubicin, the FDA label for PLD includes a warning listing cardiotoxicity. Our objective was to evaluate predictors of pre- and post-treatment cardiac testing and quantify the effect of PLD on cardiac function in patients treated for gynecologic malignancies.

Methods: Retrospective chart review of gynecologic oncology patients who received PLD over a 10-year period at a single institution. Cardiac studies were aligned to PLD treatment and ejection fractions (EF) were compared pre- and post-treatment.

Results: A total of 453 patients who had received PLD were identified; 216 (48 %) had pre-PLD treatment cardiac function testing. Predictors of pre-chemotherapy testing were diabetes ($p = 0.015$), higher ECOG score ($p = 0.004$), and cardiac disease ($p = 0.032$). Eighty-three (18.3 %) patients had pre- and post-PLD treatment cardiac function testing. Predictors of pre- and post- testing were number of cycles of PLD ($p < 0.0001$) and total dose of PLD ($p < 0.0001$). Seventy-five (90 %) patients had no change in EF (defined as < 10 %), while 2 (2.4 %) had improvement in EF > 10 %, and 6 (7.2 %) had a decrease in EF > 10 %. Initial EF in patients with > 10 % decrease was higher than in those without change or improvement ($p = 0.0004$). One (1.2 %) patient had a clinically significant decrease in EF (32.5 %) resulting in interruption of treatment.

Conclusion: Risk of cardiac toxicity from administration of PLD for patients undergoing treatment for gynecologic cancers appears to be low. Selective screening of cardiac function should be employed for these patients.

1. Introduction

Pegylated liposomal doxorubicin (PLD), a liposomal formulation of doxorubicin, is approved for use in gynecologic malignances, including ovarian and uterine cancer, as well as breast cancer, multiple myeloma, and Kaposi's sarcoma (Gabizon et al., 2016; NCCN Clinical Practice Guidelines in Oncology, 2024; NCCN Clinical Practice Guidelines in Oncology, 2024; Wagner et al., 2012; Yuan et al., 2021). This pegylated formulation of doxorubicin, which is encapsulated within liposomes and coated with a polyethylene glycol (PEG) layer, results in prolonged circulation time as well as improved targeting of tumor tissue (Drummond et al., 1999). Traditional doxorubicin metabolite leads to production of free radicals in tissues, which poses a particular threat for myocardial tissue as it is unable to effectively scavenge free radicals and does not undergo regeneration (Li et al., 2022). Compared to non-liposomal doxorubicin (Chatterjee et al., 2010), PLD offers decreased cardiotoxicity because the liposomes are unable to penetrate healthy tissue capillaries in organs such as the heart, but are able to penetrate tumor tissue capillaries due to their increased permeability (Li et al., 2022; Allen and Martin, 2004; O'Brien et al., 2004; Smith et al., 2010).

Although an endomyocardial biopsy is the gold standard to diagnose cardiotoxicity, this method is invasive and impractical (Berry et al., 1998). Therefore, the preferred modality of cardiac imaging to assess cancer therapy-related cardiac dysfunction is a transthoracic echocardiogram, with second and third options being cardiac magnetic resonance (CMR) and nuclear medicine imaging (MUGA), respectively (Lyon et al., 2022). The definition of cancer therapy-related cardiac dysfunction differs depending on the study in question, however, the most common objective measure to assess cardiac function remains the left ventricular ejection fraction (EF) and/or global longitudinal strain. The

* Corresponding author at: Cedars-Sinai Medical Center, 8635 W 3rd Street, Suite 160-W, Los Angeles, CA 90048, USA.
E-mail address: khrystyna.levytska@cshs.org (K. Levytska).

https://doi.org/10.1016/j.gore.2025.101727
Received 17 January 2025; Received in revised form 13 March 2025; Accepted 15 March 2025
Available online 17 March 2025

change in EF which constitutes cardiotoxicity varies amongst studies and is generally defined between 5 to 20 % decrease for low-grade toxicity (O'Brien et al., 2004; Lyon et al., 2022; Herrmann et al., 2022; Homesley et al., 1992; DOXIL, 1995; Parashar et al., 2023).

Despite evidence that PLD harbors less cardiotoxicity than traditional doxorubicin (Smith et al., 2010; Ibrahim et al., 2022), the FDA label includes a black box warning listing risk of cardiotoxicity and heart failure, particularly as the cumulative dose approaches 550 mg/m^2, and recommends assessment of cardiac function during treatment with PLD (DOXIL, 1995). Current requirements for routine cardiac function testing result in unnecessary testing, cost, and inconvenience for the patient (Kushnir et al., 2015). Several small retrospective chart review studies (7 and 56 patients) evaluated cardiotoxicity of PLD in the gynecologic oncology population and concluded the lack of significant negative impact of PLD on cardiac function in this patient population, even with cumulative doses of PLD exceeding 400 mg/m^2 (Dioun et al., 2019; Kesterson et al., 2010). Furthermore, prolonged use of PLD (≥6 cycles) has not been shown to be associated with heart failure in a study of 22 gynecologic oncology patients (Uyar, 2004).

Given that there are no large-scale studies examining the effect of PLD on cardiac function in patients with gynecologic malignancies, we aimed to determine factors which predict the likelihood of patients receiving pre- and post-treatment cardiac function testing, as well as evaluate the change in left ventricular ejection fraction (EF) over the course of PLD use.

2. Methods

The study was an IRB-approved retrospective chart review (IRB#07–20-17E) of gynecologic oncology patients undergoing treatment with PLD between 2010 and 2020 at a single institution (Charlotte, NC, USA). The institutional pharmacy database identified patients receiving PLD during the study period; this was then narrowed by using diagnosis codes of gynecologic (uterine, ovarian, cervical, fallopian tube, or primary peritoneal) malignancies. Patient demographics, medical co-morbidities, chemotherapy regiments, PLD doses, number of cycles, and cardiac imaging results were collected. Cardiac evaluations in the form of transthoracic echocardiogram or nuclear medicine (multigated acquisition or MUGA) scans were included. An echocardiogram was the most common modality of cardiac testing in our population and left ventricular EF was used as a surrogate marker for cardiac function. Where a range in EF was reported in a study, the final number recorded was the average. We defined difference of > 10 % between initial cardiac testing and follow up testing as "significant," in order to capture any changes in EF during the treatment course resulting in cardiotoxicity, as the majority of patients had no changes in EF. Cardiac function testing was aligned to PLD chemotherapy treatments and EF values were compared before and after treatment. Change in cardiac function was calculated as a difference between starting EF and EF following treatment. The first cardiac evaluation following the last PLD treatment was recorded as a "post-treatment" assessment.

Descriptive statistics were used to describe patient characteristics, PLD treatment doses and cycle numbers, and reported as number (n, %), mean ± SD, or median [IQR]. Parametric and non-parametric tests were used where appropriate. Logistic regression model was used to determine predictors of cardiac testing before and after treatment with PLD. Significance level $p < 0.05$ was set for all analyses. All statistical analyses were conducted using the SAS software, Version 9.4.

3. Results

Patient characteristics are shown in Table 1. A total of 453 patients were included in the study. The mean cumulative PLD dose was 277 ± 162.5 mg/m^2 (range 40–1,120 mg/m^2) over a median of 4 [2-6] cycles (Supplementary Fig. 1). Only 25 patients (3.5 %) received > 550 mg/m^2. Across the entire cohort, 216 (48 %) patients had pre-treatment cardiac evaluation and 83 (18 %) had pre- and post-treatment cardiac testing. Of the 453 patients, 371 (81.9 %) were deceased and 69 (15.2 %) were living at the time of data collection. Patients were predominantly White (338, 74.6 %) or Black (86, 20.0 %). Primary malignancy sites were ovary (197, 43.5 %) and uterus (119, 26.3 %). The majority of patients had Eastern Cooperative Oncology Group (ECOG) scores of 0 (394, 87.0 %) or 1 (38, 8.4 %). In terms of co-morbidities, 222 (49 %) of patients had hypertension, 71 (15.7 %) had diabetes, 41 (9.1 %) were classified as obese (BMI > 30), and only 7 (1.5 %) had reported cardiac disease. Patient ethnicity distribution, primary malignancy site, ECOG at diagnosis, and co-morbidities are listed in Table 1, stratified by availability of pre- and post-PLD treatment cardiac testing.

Results of cardiac function testing are shown in Table 2. The vast majority of initial cardiac testing was performed via a transthoracic echocardiogram (195, 90.3 %), while nuclear medicine scans were

Table 1
Patient characteristics. Total 453 patients were included in analysis, 216 patients these had pre-PLD cardiac testing, and 83 patients had pre- and post-treatment cardiac evaluation. Majority of patients were Caucasian, had ovarian cancer, and had a ECOG performance status of 0 at diagnosis. Hypertension was the most common comorbidity. Obesity defined as BMI > 30. ECOG, Eastern Cooperative Oncology Group; PLD, pegylated liposomal doxorubicin. Values expressed as n (%).

Parameter	All patients (n = 453)	Patients with pre-PLD testing (n = 216)	Patients with pre- and post-PLD testing (n = 83)
Ethnicity			
White	338 (74.6 %)	163 (75.5 %)	62 (74.7 %)
Black/African American	86 (20.0 %)	40 (18.5 %)	19 (22.9 %)
South Asian	9 (2.0 %)	4 (1.9 %)	2 (2.4 %)
Native American	8 (1.8 %)	4 (1.9 %)	0 (0 %)
Hispanic	3 (0.7 %)	1 (0.1 %)	0 (0 %)
Other/unknown	9 (2.0 %)	4 (1.9 %)	0 (0 %)
Primary malignancy site			
Ovary	197 (43.5 %)	83 (38.4 %)	34 (41.0 %)
Uterus	119 (26.3 %)	69 (31.9 %)	23 (27.7 %)
Fallopian tube	80 (17.7 %)	43 (19.9 %)	15 (18.1 %)
Primary peritoneal	46 (10.2 %)	16 (7.4 %)	9 (10.8 %)
Unknown	11 (0.02 %)	5 (2.3 %)	2 (0.02 %)
ECOG performance status at diagnosis			
0	394 (87.0 %)	177 (81.9 %)	70 (84.3 %)
1	38 (8.4 %)	26 (12.0 %)	11 (13.2 %)
2	7 (1.5 %)	5 (2.3 %)	0 (0 %)
3	3 (0.7 %)	0 (0 %)	0 (0 %)
Unknown	11 (2.4 %)	8 (3.7 %)	2 (2.4 %)
Comorbidities			
Hypertension	222 (49 %)	112 (51.9 %)	40 (48.2 %)
Diabetes	71 (15.7 %)	43 (19.9 %)	17 (20.5 %)
Obesity	41 (9.1 %)	15 (6.9 %)	4 (4.8 %)
Cardiac disease	7 (1.5 %)	6 (2.8 %)	3 (3.6 %)

Table 2
Cardiac evaluation modality and PLD dosing in patient with pre-treatment testing alone and those with pre- and post-treatment cardiac testing. Majority of patients were evaluated by a transthoracic echocardiogram, with a small proportion evaluated by a nuclear medicine scan. NM, nuclear medicine; PLD, pegylated liposomal doxorubicin; TTE, transthoracic echocardiogram. Values expressed as n (%), mean ± SD, or median [IQR].

Parameter	Patients with pre-PLD cardiac function testing (n = 216)	Patients with pre- and post-PLD cardiac function testing (n = 83)
Cardiac testing modality		
Pre-TTE	195 (90.3 %)	76 (91.6 %)
Pre-NM scan	21 (9.7 %)	7 (8.4 %)
Post-TTE	–	77 (92.8 %)
Post-NM scan	–	6 (7.2 %)

recorded in 21 (9.7 %) of patients with pre-treatment cardiac testing only. Similarly, of the patients with both pre- and post-PLD cardiac testing, 76 (91.6 %) had transthoracic echocardiogram as a cardiac testing modality, while 7 (8.4 %) had a nuclear medicine scan. Pre-treatment cardiac testing modality differed from the post-treatment testing modality in 5 (6 %) of patients. The group of patients with pre-treatment cardiac testing only received an mean cumulative dose of 304.5 ± 187.8 mg/m^2 of PLD over a median of 4 [3-6] cycles (Supplementary Fig. 2A). The group of patients who had both pre- and post-PLD cardiac function testing received an average of 372.6 ± 211.8 mg/m^2 of PLD over a median of 5 [3-7] cycles before their subsequent cardiac function test (Supplementary Fig. 2B). The median number of months between the last PLD treatment and subsequent cardiac testing was 2 [0–5.5] months.

Predictors of cardiac testing in our gynecologic oncology patient population are shown in Table 3. Higher ECOG score (LR 13.3, p = 0.0047), diabetes (LR 6.0, p = 0.0146), and cardiac disease (LR 4.6, p = 0.0322) were all significantly associated with receiving cardiac testing prior to initiation of PLD administration. Hypertension and obesity were not associated with pre-chemotherapy testing. Predictors of pre- and post-chemotherapy cardiac function testing were also evaluated. The only predictors of pre- and post-treatment testing were the number of cycles of PLD (LR 12.3, p < 0.0001) and total dose of PLD (LR 15.5, p < 0.0001). Initial EF, BMI, ECOG status, hypertension, obesity, diabetes, cardiac disease did not predict cardiac evaluation before and after PLD treatment (p > 0.05 for all).

Next, changes in EF following treatment with PLD were evaluated in 83 patients who had pre- and post-treatment cardiac testing available. The mean change in EF across this cohort was an overall 1.6 ± 8.1 % improvement. Patients were further separated into three groups: patients without any change in EF (defined as < 10 % change in either direction), patients with > 10 % increase in EF, and patients with > 10 % decrease in EF. Overall, 75 (90.4 %) of patients had no change in EF between pre- and post-treatment testing, 2 (2.4 %) patients showed improvement (>10 % increase), and 6 (7.2 %) patients showed worsening (>10 % decrease). The initial EF for patients without any change was 59.5 ± 0.6 %. Those patients with an increase in EF by more than 10 % had an initial EF 45.5 ± 3.6 %, while patients with a decrease in EF by more than 10 % had an initial EF 62.8 ± 2.1 % (p = 0.004). There were no differences between groups in number of cycles of PLD received, total dose of PLD administered, rates of hypertension, obesity, diabetes, or cardiac disease. One patient had a clinically significant decrease in EF (32.5 %) which led to an interruption of treatment. Her echocardiogram was obtained 1 month after completion of 9th cycle with a total PLD dose of 630 mg/m^2. This patient had a primary diagnosis of Stage IIB uterine carcinosarcoma, and had other co-morbidities, including substance abuse and hepatitis C.

Table 3
Predictors of pre-treatment cardiac evaluation alone and pre- and post-treatment cardiac function testing. Predictors of pre-treatment testing only were a higher ECOG score, diabetes mellitus, or cardiac disease. Predictors of pre- and post-treatment testing were the number of cycles of PLD and total dose of PLD received. Obesity defined as BMI > 30. ECOG, Eastern Cooperative Oncology Group; EF, ejection fraction; LR, likelihood ratio; PLD, pegylated liposomal doxorubicin. Significance set as p < 0.05 (*).

Parameter	Patients with pre-PLD cardiac function testing (n = 216)		Patients with pre- and post-PLD cardiac function testing (n = 83)	
	LR	P value	LR	P value
Higher ECOG score	13.3	p = 0.0047*	6.7	p = 0.0833
Diabetes	6.0	p = 0.0146*	1.8	p = 0.1808
Cardiac disease	4.6	p = 0.0322*	2.3	p = 0.1274
Hypertension	1.7	p = 0.4375	0.4	p = 0.8175
Obesity	2.2	p = 0.1376	2.5	p = 0.1118
Total PLD dose (mg/m^2)			15.5	p < 0.0001*
Number of cycles			12.3	p < 0.0001*
Initial EF	–	–	1.3	p = 0.1064

4. Conclusions

Our study identified predictors of cardiac function testing for patients undergoing treatment with PLD and examined the effects of PLD on cardiac function in a gynecologic oncology patient population. In our cohort, pre-PLD treatment cardiac imaging was obtained in almost half of the patients. Predictors of pre-treatment testing were higher ECOG score, diabetes, and cardiac disease. Almost 20 % of patients had pre- and post-PLD treatment cardiac testing. Predictors of cardiac testing for both pre- and post-treatment were the number of cycles of PLD administered and the total cumulative dose of PLD received. On average, there was no change in EF following treatment with PLD. Most patients (90 %) had no change in EF, and only one patient had a significant symptomatic EF drop which required discontinuation of chemotherapy. Of 83 patients who had pre- and post-PLD treatment cardiac evaluation, the mean dose of PLD was 373 mg/m^2 over a median of 5 cycles. The manufacturers of PLD caution against exceeding the maximum cumulative dose of PLD (550 mg/m^2); and the majority of the gynecologic oncology patients in our study and other studies are usually within that limit (Kushnir et al., 2015). Although most patients in our study had no change in EF, 7.2 % had a decrease in EF by more than 10 %. Notably, the patients who had a decrease in EF that we considered significant (i.e., more than 10 %) had a significantly higher initial EF prior to treatment initiation. This finding could be interpreted as a normalization of EF, rather than a clinically significant decrease or cardiotoxicity.

PLD is a chemotherapy regimen often used alone or in combination for treatment of ovarian and other gynecologic malignancies. This liposomal formulation of doxorubicin offers improved tissue targeting and significantly less cardiac toxicity (Drummond et al., 1999; Allen and Martin, 2004; Smith et al., 2010). Despite this, the FDA access sheet for PLD contains a black box warning of cardiotoxicity and recommends routine screening for cardiac toxicity of PLD, especially as the cumulative dose approaches 550 mg/m^2, although the FDA does not provide guidelines on the exact timing of cardiac testing, apart from mentioning baseline testing, testing during treatment to detect acute changes, and testing after treatment to detect delayed cardiomyopathy (DOXIL, 1995). Current literature lacks large-scale studies evaluating the effect of PLD on cardiac function in the gynecologic oncology population. Studies pertaining to gynecologic malignancies have been reported, however, are mostly limited by number of patients (Kushnir et al., 2015; Dioun et al., 2019; Kesterson et al., 2010; Uyar, 2004). One study reported on 7 patients who had received a cumulative dose of PLD > 400 mg/m^2 and had cardiac testing before and after PLD treatment (Kesterson et al., 2010). The authors found no clinical evidence of cardiotoxicity which resulted in interruption or discontinuation of treatment. Another group described 46 patients who had underwent treatment with PLD and had pre- and post-treatment cardiac surveillance (Dioun et al., 2019). Three patients had a decrease in EF, and only one of these patients required an interruption in treatment. These patients had received between 144 and 1,898 mg/m^2 cumulative dose of PLD with resulting decrease in EF ranging from 10 to 35 %. Others still have shown no effect of PLD on cardiac function, even when patients receive PLD for a prolonged treatment course (≥6 cycles) (Uyar, 2004) or have risk factors for anthracycline-induced cardiotoxicity (Kushnir et al., 2015).

Our study adds to the growing literature of retrospective cohorts supporting the lack of clinically meaningful manifestation of PLD-related cardiac dysfunction in the gynecologic oncology patient population, and contains the largest population of gynecologic oncology patients undergoing treatment with PLD screened for availability of cardiac testing results. Nonetheless, our study has several limitations, some of which are inherent to the nature of our study design. Timing of cardiac surveillance was not standardized across our cohort, and only 1

in 5 patients had testing before and after treatment with PLD. In addition, any cardiac testing performed outside of our electronic medical record system could not be captured given lack of access to this data. Although median number of months from last treatment dose until first cardiac assessment was short (2 months), we are not able to account for any potential or actual events or insults that could have occurred between the last treatment and next available cardiac function evaluation. The optimal time to capture changes in EF following PLD administration is unknown, although for doxorubicin, studies show cardio-toxic effects on cardiac function varies from early and on treatment to late and off treatment (Smith et al., 2010). Furthermore, only half of patients in our cohort who received PLD had cardiac evaluation prior to the initiation of treatment. Comparison of our findings to other studies is challenging given overall heterogeneity, sample size, and retrospective nature of published literature. Some authors have reported majority of patients (>90 %) having baseline cardiac testing, despite only 17 % moving on to have subsequent imaging throughout the treatment course (Kesterson et al., 2010), while others outlined a selective cardiac testing algorithm for patients with only high-risk features resulting in 15 % of patients receiving cardiac surveillance during treatment (Kushnir et al., 2015). Our observed number of patients who had undergone baseline cardiac surveillance could be due to factors such as unavailability of records in a retrospective chart review study or changes in clinical practice overtime towards omitting cardiac testing.

Patients with certain co-morbidities, such as hypertension, pre-existing cardiovascular disease, peripheral vascular disease, and others, are more likely to develop anthracycline-associated cardiotoxicity (Smith et al., 2010). Having these risk factors likely prompts providers to perform baseline cardiac testing for patients receiving PLD by extrapolation of doxorubicin guidelines. We found higher ECOG score, diabetes, and presence of cardiac disease to be predictors of cardiac function assessment prior to initiation of treatment with PLD. Similarly, patients with increasing number of cycles and cumulative dose of PLD were more likely to undergo surveillance of cardiac function as they went through treatment. We found that the vast majority of patients, even those with the aforementioned risk factors, did not exhibit significant cancer therapy-associated cardiac dysfunction while on treatment with PLD. Others have found that routine cardiac surveillance for all patients is not cost-effective, and PLD-induced heart failure is extremely rare, even in patients with high-risk features for anthracycline-induced cardiotoxicity (i.e., advanced age, prior mediastinal irradiation, and prior anthracycline exposure, and others) (Kushnir et al., 2015). Approximating the cost of cardiac testing methods, such as echocardiogram or MUGA, has its challenges in the US healthcare system, however, one study found savings of nearly $200,000 USD when a selective cardiac evaluation algorithm (15 % of 184 patients) was used in a gynecologic oncology patient population receiving PLD in North Carolina and Maryland (Kushnir et al., 2015). Currently, the American Society of Clinical Oncology (ASCO) and Society of Gynecologic Oncology (SGO) do not have consensus statements on cardiac surveillance in patients receiving PLD, apart from mentioning that PLD can be considered for patients with abnormal cardiac function who would otherwise be receiving doxorubicin (Armenian et al., 2017; Society of Gynecologic Oncology, 2023).

In summary, we found that PLD carries a low risk of cardiotoxicity in patients being treated for gynecologic malignancies. We conclude that routine screening of cardiac function before, during, and after treatment with PLD should be used sparingly and limited to patients exhibiting signs or symptoms of cardiac dysfunction. Prospective studies aimed at understanding the extent of PLD effect on cardiac function and the impact on nation-wide healthcare cost savings can help drive care for our patients in the future.

CRediT authorship contribution statement

Khrystyna Levytska: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Data curation, Conceptualization. **R. Wendel Naumann:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **Miranda J. Benfield:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Jubilee Brown:** Writing – review & editing, Writing – original draft, Conceptualization. **Yovanni Casablanca:** Writing – review & editing, Writing – original draft, Conceptualization. **Brittany Lees:** Writing – review & editing, Writing – original draft, Conceptualization. **Allison M. Puechl:** Writing – review & editing, Writing – original draft, Conceptualization. **Erin K. Crane:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Funding

No funding sources were used.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to acknowledge the following for assistance with this project and study: Gynecologic Oncology Division, Research Committee and staff, Dr. Julio Mateus-Nino, Mary H. Andrews, Deanna S. Hamm, Gretchen L. Hoelscher; patients and their families, and research support staff at Atrium Health.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2025.101727.

References

Allen, T.M., Martin, F.J., 2004. *Advantages of liposomal delivery systems for anthracyclines.* Semin. Oncol. 31 (6 Suppl 13), 5–15.
Armenian, S.H., et al., 2017. *Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline.* J. Clin. Oncol. 35 (8), 893–911.
Berry, G., et al., 1998. *The use of cardiac biopsy to demonstrate reduced cardiotoxicity in AIDS Kaposi's sarcoma patients treated with pegylated liposomal doxorubicin.* Ann. Oncol. 9 (7), 711–716.
Chatterjee, K., et al., 2010. *Doxorubicin cardiomyopathy.* Cardiology 115 (2), 155–162.
Dioun, S.M., et al., 2019. *Necessity of routine cardiac evaluation in patients receiving pegylated liposomal doxorubicin for gynecologic cancer.* Gynecol. Oncol. 155 (2), 301–304.
DOXIL® (doxorubicin HCl liposome injection) for intravenous infusion Initial U.S., 1995; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/050718s029lbl.pdf.
Drummond, D.C., et al., 1999. *Optimizing liposomes for delivery of chemotherapeutic agents to solid tumors.* Pharmacol. Rev. 51 (4), 691–743.
Gabizon, A.A., Patil, Y., La-Beck, N.M., 2016. *New insights and evolving role of pegylated liposomal doxorubicin in cancer therapy.* Drug Resist. Updat. 29, 90–106.
Herrmann, J., et al., 2022. *Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement.* Eur. Heart J. 43 (4), 280–299.
Homesley, H.D., et al., 1992. *Randomized comparison of cisplatin plus epirubicin or doxorubicin for advanced epithelial ovarian carcinoma. A multicenter trial.* Am. J. Clin. Oncol. 15 (2), 129–134.
Ibrahim, M., et al., 2022. *Encapsulation, Release, and Cytotoxicity of Doxorubicin Loaded in Liposomes, Micelles, and Metal-Organic Frameworks: A Review.* Pharmaceutics 14 (2).
Kesterson, J.P., Odunsi, K., Lele, S., 2010. *High cumulative doses of pegylated liposomal doxorubicin are not associated with cardiac toxicity in patients with gynecologic malignancies.* Chemotherapy 56 (2), 108–111.
Kushnir, C.L., et al., 2015. *Selective cardiac surveillance in patients with gynecologic cancer undergoing treatment with pegylated liposomal doxorubicin (PLD).* Gynecol. Oncol. 137 (3), 503–507.
Li, X.R., et al., 2022. *Cardiac safety analysis of first-line chemotherapy drug pegylated liposomal doxorubicin in ovarian cancer.* J Ovarian Res 15 (1), 96.

Lyon, A.R., et al., 2022. *2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS)*. Eur. Heart J. 43 (41), 4229–4361.

NCCN Clinical Practice Guidelines in Oncology, T., 2024. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer, Version 3.2024. National Comprehensive Cancer Network.

NCCN Clinical Practice Guidelines in Oncology, T., 2024. Uterine Neoplasms, *Version 3.2024*. National Comprehensive Cancer Network.

O'Brien, M.E., et al., 2004. *Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer*. Ann. Oncol. 15 (3), 440–449.

Parashar, S., et al., 2023. *Cancer Treatment-Related Cardiovascular Toxicity in Gynecologic Malignancies: JACC: CardioOncology State-of-the-Art Review*. JACC CardioOncol 5 (2), 159–173.

Smith, L.A., et al., 2010. *Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials*. BMC Cancer 10, 337.

Society of Gynecologic Oncology, T., 2023. SGO, FWC and GOG-F* Communique: Considerations When Treating Persons with Gynecologic Cancers in the Setting of Pegylated Liposomal Doxorubicin Shortages. September 7.

Uyar, D., et al., 2004. *Cardiac safety profile of prolonged (>or=6 cycles) pegylated liposomal doxorubicin administration in patients with gynecologic malignancies*. Gynecol. Oncol. 94 (1), 147–151.

Wagner, U., et al., 2012. *Final overall survival results of phase III GCIG CALYPSO trial of pegylated liposomal doxorubicin and carboplatin vs paclitaxel and carboplatin in platinum-sensitive ovarian cancer patients*. Br. J. Cancer 107 (4), 588–591.

Yuan, Z., et al., 2021. *Pegylated liposomal doxorubicin in patients with epithelial ovarian cancer*. J Ovarian Res 14 (1), 12.