



A Review of Cardiac Safety Surveillance in Breast and Ovarian Cancer Patients Receiving Pegylated Liposomal Doxorubicin (PLD): Cardiac Biomarkers, Neutrophil-to-Lymphocyte Ratio (NLR) and the Role of Pharmacist-Led Cardio-Oncology Counseling

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ABSTRACT :

Pegylated liposomal doxorubicin (PLD) is an anthracycline used in the management of breast and ovarian cancers. Compared with conventional doxorubicin, PLD provides comparable anticancer efficacy with reduced cardiotoxicity; however, the risk of cardiovascular complications is not completely eliminated, particularly in patients with previous anthracycline exposure or cardiovascular risk factors. Therefore, cardiovascular risk assessment and monitoring are important during PLD therapy. Echocardiography, global longitudinal strain, cardiac troponin, and natriuretic peptides are commonly used for cardiac surveillance and may help in the early identification of cardiac injury. The neutrophil-to-lymphocyte ratio (NLR), obtained from a complete blood count, is an easily accessible marker of systemic inflammation and may provide additional information regarding cardiovascular risk, although its specific role in PLD-induced cardiotoxicity remains uncertain. Pharmacist-led cardio-oncology counseling may support patients by improving medication adherence, recognition of cardiac symptoms, understanding of monitoring requirements, and communication with oncology and cardiology teams. This review focuses on the cardiac safety profile of PLD in breast and ovarian cancer patients, the role of cardiac biomarkers and NLR in cardiac surveillance, and the contribution of pharmacists to patient education and monitoring. Although PLD has a more favorable cardiac safety profile than conventional doxorubicin, continued surveillance remains important. Baseline cardiovascular risk assessment, echocardiographic evaluation, biomarker monitoring, and regular follow-up can support early recognition of cardiovascular complications. NLR may be considered an exploratory inflammatory marker, but prospective research is required to establish its predictive value. Pharmacist-led counseling may complement cardio-oncology care by promoting patient awareness, adherence, symptom recognition, and appropriate referral.

Introduction

Breast and ovarian cancers are a considerable portion of all cancers in women around the world, [1,2] and among Indian women breast cancer is the commonest cancer in females. [3] The improved survival seen in breast cancer cases and the protracted course of recurrent ovarian cancers ensure that many patients survive to encounter the late cardiovascular sequelae of their treatments. [4,5] Current guidelines also consider cardiovascular well-being as an essential component of oncology practice. [6,7]. Anthracyclines continue to be effective drugs in both malignancies, although doxorubicin is associated with dose-related cardiomyopathy, which in a pooled retrospective study of three trials showed a steep increase in the incidence of congestive heart failure according to dose. [8] Potential mechanisms include DNA damage caused by topoisomerase II- β in cardiomyocytes, as well as mitochondrial toxicity and oxidative stress. [9,10,11] The cardiotoxicity may occur acutely, during early treatment, or after many years, and risk factors include age, hypertension, diabetes, previous cardiac disease, prior anthracyclines or trastuzumab use and left chest radiotherapy. [5,12,13] Pegylated liposomal doxorubicin was created to change its distribution and reduce myocardial uptake. The liposomes persist in circulation and myocardial uptake is minimal while their uptake by tumors is maximal. [14,15] In a randomized study in metastatic breast cancer, PLD was associated with similar efficacy and significantly less cardiac toxicity than standard doxorubicin. [16] Meta-analysis also showed less cardiotoxicity than conventional anthracyclines. [17,18] Pegylated liposomal doxorubicin is approved for taxane-resistant breast cancer and recurrent ovarian cancer in combination with carboplatin. [19,20,21,22,23,24,25]. Its principal dose-limiting toxicities are palmar-plantar erythrodysesthesia and stomatitis and not heart failure. [26,27,28] Reduced does not mean absence. There are patients who were on anthracyclines, taxanes, trastuzumab, or chest radiation prior to PLD, while older ovarian cancer patients tend to be comorbid with cardiovascular disease. [4,6] For this reason, risk stratification at baseline and subsequent

surveillance based on risk using echocardiography with strain imaging and cardiac biomarkers like troponin and natriuretic peptides is recommended. [6,7,12,29] Early elevation of the biomarkers was proven to be t

he predictor of future ventricular dysfunction, [30,31] and initiation of cardioprotective therapy right after early injury resulted in better recovery of the ejection fraction. [32] In limited-resource conditions, simple indices from a complete blood count could provide additional information. Neutrophil-to-Lymphocyte Ratio (NLR) is an index of systemic inflammatory response, [33,34] prognostic of survival in various solid tumors including breast cancer, [35,36,37] as well as cardiovascular outcomes and mortality outside oncology. [38,39] It was proven that inflammation contributes both to tumor progression and treatment tolerance. [40,41] Information provided by NLR regarding cardiac risk for PLD patients remains to be seen. Counseling with teach-back technique improves patient understanding of the information, while oncology pharmacists are already involved in regimen verification and supportive care management. [42,43,44]

2. PLD in Breast and Ovarian Cancer

Important trials are listed in Table 1. In first-line metastatic breast cancer, PLD was equivalent to doxorubicin in progression-free survival with substantially lower incidence of cardiotoxicity. [16] Taxane-refractory disease has also been managed with PLD. [19] In ovarian cancer, PLD has been studied against topotecan, [20] against gemcitabine in platinum-resistant disease, [22] as the backbone of chemotherapy in AURELIA trial, [23] and together with carboplatin was superior to paclitaxel-carboplatin in platinum-sensitive late recurrence in terms of progression-free survival. [21] Recommendations include liposomal anthracyclines as treatment options for advanced disease. [24,25]

Table 1. Selected randomized trials of PLD with cardiac and other toxicity signals

Trial / setting	Comparison	Main efficacy finding	Notable toxicity pattern
O'Brien 2004; first-line MBC [16]	PLD vs doxorubicin	Comparable PFS and OS	Significantly fewer cardiac events; less alopecia and myelosuppression; more PPE and mucositis
Keller 2004; taxane-refractory MBC [19]	PLD vs vinorelbine or MMC + vinblastine	Similar PFS	PPE and stomatitis characteristic of PLD
Gordon 2001; recurrent ovarian [20]	PLD vs topotecan	PLD active; favourable in platinum-sensitive subgroup	Less hematologic toxicity; PPE and stomatitis more frequent
Mutch 2007; platinum-resistant ovarian [22]	Gemcitabine vs PLD	No PFS advantage for gemcitabine	PLD: PPE, mucositis; gemcitabine: more hematologic toxicity
CALYPSO 2010; platinum-sensitive ovarian [21]	PLD + carboplatin vs paclitaxel + carboplatin	PFS favoured PLD-carboplatin	Less neuropathy and alopecia; more PPE, mucositis, thrombocytopenia

MBC, metastatic breast cancer; PFS, progression-free survival; OS, overall survival; MMC, mitomycin C. Qualitative summary; consult original reports for effect sizes.

3. Anthracycline-induced cardiotoxicity and cardiac safety of PLD

3.1 Mechanisms

Doxorubicin-induced cardiotoxicity occurs through topoisomerase II- β -dependent DNA double-strand breaks and mitochondrial damage in cardiomyocytes with the production of reactive oxygen species, calcium dysregulation and apoptosis. [9,10,11] The damage accumulates and is often asymptomatic until the compensatory capacity becomes depleted. [5,12] Evidence from retrospective studies indicates that the risk for heart failure with traditional doxorubicin increases with cumulative dose. [8]

Why is PLD less toxic, and what risks persist?

PEGylated liposomes circulate without significant permeability into normal cardiac capillaries, reducing cardiac exposure. [14,15] Clinical studies have found it to be associated with reduced cardiotoxicity compared with doxorubicin, [16,17,18] although the evidence is based on selected trial subjects, and longitudinal follow-up of patients with preexisting cardiotoxicity is not well-developed. [4,18] Current recommendations still call for baseline risk stratification in all patients treated with any form of anthracyclines, taking previous exposures and comorbid conditions into account. [6,13]

3.3 Definitions

Cardiotoxicity has been frequently described as a reduction in left ventricular ejection fraction (LVEF), typically by at least 10% to a level less than 50%, with recent guidelines incorporating reductions in global longitudinal strain (GLS) and biomarkers for milder definitions of cardiotoxicity. [6,12,29] Cardiac adverse event classification has been performed using CTCAE. [50]

4. Imaging and Biomarker surveillance

Table 2 lists the various modalities used for this purpose. The echocardiographic LVEF assessment is the gold-standard baseline measurement, but it is a late measurement tool; however, GLS is an early detector of dysfunction. [29,51] Early increase in cardiac troponins has been observed in individuals with cardiotoxic insult, and cardiac troponins have helped predict later dysfunction in individuals undergoing anthracycline chemotherapy treatment, [30,31] and with early detection with heart failure management, there was improvement in the LVEF with earlier commencement of treatment. [32] Natriuretic peptides can also be utilized in such cases, although with less predictive power. [7,31]

Table 2. Surveillance tools for anthracycline-related cardiotoxicity

Tool	Role	Practical considerations
Echocardiographic LVEF [12,29]	Standard baseline and follow-up functional measure	Late marker; operator dependent; widely available
Global longitudinal strain [29,51]	Detects subclinical dysfunction; relative decline used in guidelines [6]	Needs standardized vendor-consistent measurement and training
Troponin [30,31,32]	Early marker of myocardial injury	Timing relative to dose matters; assay sensitivity varies
Natriuretic peptides (BNP/NT-proBNP) [7,31]	Marker of wall stress and heart-failure risk	Affected by age, renal function, obesity, anemia
Baseline risk score (HFA-ICOS) [6,13]	Stratifies patients into low, medium, high, very high risk	Guides frequency of surveillance and need for cardiology referral
NLR (exploratory) [33,38,39]	Inflammatory context; not validated for cardiotoxicity	Confounded by steroids, infection, neutropenia [52,53]

LVEF, left ventricular ejection fraction; HFA-ICOS, Heart Failure Association–International Cardio-Oncology Society risk tool.

5. NLR: The Rationale and Limitations

The neutrophil-lymphocyte ratio is the absolute neutrophil count over the absolute lymphocyte count and encompasses cytokine-induced neutrophilia and stress-associated lymphopenia. [33,34] Healthy adult NLR levels are typically quoted between 1 and 3; the cut-off values depend on the studied population. [52] In oncology, high NLR has poor prognosis among different cancers, including breast cancer, [35,36] despite heterogeneity and risk of bias reported in a recent umbrella review. [37] Higher neutrophil proportions and NLR were associated with increased risk of cardiovascular morbidity and mortality following myocardial infarction in non-oncology populations. [38,39] Chronic inflammation is mechanistically connected to cardiovascular disease as well. [40,41]. This evidence base supports consideration of NLR as a potential marker of underlying cardiovascular and inflammatory predisposition but not as a predictor of PLD-induced cardiotoxicity. Pre-medication with corticosteroids, infections, neutropenia, tumor burden, and variability of laboratory measurements complicate interpretation, [41,52,53] and change from the patient's baseline may be more relevant than a particular threshold level. [37]

6. Suggested Risk-Adapted Approach

It is suggested that pharmacists perform screening for every patient prior to PLD for assessment of the baseline cardiovascular risk (with a use of a tool like HFA-ICOS when it is possible), [6,13] assessment of cardiotoxic history and anthracycline cumulative doses, [8,12] and assessment of the blood pressure level, medication list, troponin/natriuretic peptides, and echocardiography results where applicable to the institution. The NLR trend is introduced as an exploratory inflammatory context marker. See Table 3.

Table 3. Conceptual risk-adapted pathway (hypothesis-generating; NLR component exploratory)

Baseline risk	Typical features	Suggested pharmacist-led actions (with oncology and cardiology teams)
Low	No prior anthracycline, normal baseline tests, no major risk factors	Standard counseling; baseline and guideline-based follow-up; record NLR baseline
Medium	Age, hypertension, prior anthracycline, borderline results [13]	Optimize blood pressure and cardiovascular medicines; consider closer biomarker or echo follow-up [6]
High / very high	Prior heart disease, prior anthracycline plus RT or trastuzumab, abnormal baseline	Early cardio-oncology referral; strict surveillance per guideline; medication review for interactions [6,7]
Any risk with new signal	Symptoms, rise in troponin or NT-proBNP, GLS decline, sustained rising NLR from baseline	Same-week clinical review; notify oncologist; cardiology assessment; consider cardioprotective therapy per specialist [6,32]

NLR rise alone should prompt review of confounders and clinical assessment, not treatment change.

7. The Pharmacist's Role

7.1 Scope

Oncology pharmacists participate in regimen validation, cumulative dose documentation, medication reconciliation, toxicity monitoring and patient education and these have been identified as key responsibilities in the literature. [42,43,44] Structured education and follow-up increase compliance and facilitate early identification of any problems. [44,45] Teach-back has proven an effective technique for verifying understanding. [46]

7.2 Counseling content

Table 4. Suggested pharmacist-led cardio-oncology counseling for patients receiving PLD

Domain	Key counseling points	Monitoring / documentation
Baseline risk review	Prior anthracycline, trastuzumab, chest RT; hypertension, diabetes, dyslipidemia, smoking [4,13]	Risk category and cumulative anthracycline dose recorded [8]
Symptom recognition	Report breathlessness, ankle swelling, palpitations, chest discomfort, unusual fatigue, fainting	Structured phone follow-up after cycles; CTCAE cardiac grading [50]
Medicines	Adherence to antihypertensives and other cardiovascular drugs; review of NSAIDs, interacting drugs and supplements [6]	Medication reconciliation each cycle
Lifestyle	Physical activity as tolerated, salt and alcohol moderation, smoking cessation, healthy weight [4]	Blood pressure and weight log
Surveillance adherence	Explain why echo and blood tests are scheduled and keep appointments [6,12]	Appointment tracking
Laboratory review	Review troponin/NT-proBNP where done, hemoglobin (anemia can worsen cardiac symptoms), and NLR trend [52,54,55]	Values and trends documented
Communication	Teach-back; written vernacular materials; contact number [46]	Documentation of understanding

NSAID, non-steroidal anti-inflammatory drug; RT, radiotherapy.

7.3 Workflow

- **Prior to cycle 1:** baseline risk assessment, medication reconciliation, cumulative dose tracking and first patient counseling session.
- **Per cycle:** evaluation of symptoms, blood pressure, lab trends and surveillance testing; reinforcement of counseling through teach-back approach.
- **Interim follow-up:** pharmacist call/visit within 1 week post-dosing for symptom and compliance check.

- **Escalation:** any cardiac symptoms, elevated biomarkers or imaging abnormalities are reported on that same day to the oncologist for cardiology consultation.

There is consistent evidence to support pharmacist interventions in oncology patients, albeit varied; however, studies related to PLD cardiac surveillance are scarce. [6,42]

8. Research Agenda

- **Study design:** Prospective multicentre cohort study involving women with breast and ovarian cancer undergoing PLD with clinical outcome endpoints of LVEF impairment, GLS reduction, increase in biomarkers, heart failure symptoms and medication discontinuation.
- **Predictors:** Risk category at baseline, exposure to drugs and medications, cumulative dose, biomarkers, NLR at baseline and dynamically, together with age, hypertension, diabetes and performance status.
- **Analysis:** Multivariate analysis with internal validation, calibration and decision curve analysis. [49]
- **Quality:** TRIPOD methodology for reporting and PROBAST risk-of-bias evaluation tool. [47,48]
- **Intervention:** Stepped wedge or randomized trial of pharmacist-led counseling vs control.
- **Thresholds:** Local cut-offs of NLR considering steroids administration schedule and laboratory analyzers. [37,52]

Limitations

This is an un-systematic narrative review, and some relevant papers could have been missed. Cardiac-related PLD-specific literature is sparse, particularly among older women and women who have received previous anthracyclines. [17,18] The idea that NLR has added predictive power in PLD-induced cardiotoxicity has not yet been validated, as far as we know; relevant studies have been conducted in other groups. [37,38,39] Tables 3 and 4 serve as initial templates only for conducting research and local protocols, but not as clinical recommendations. [6]

10. Conclusion

The use of PLD reduces but does not remove the patient's risk of cardiovascular problems; moreover, many patients taking this therapy are at risk due to other cardiovascular risks. The use of guidelines for baseline risk estimation, imaging and biomarkers allows one to identify injuries at an early stage and treat them efficiently. NLR is an easily measurable marker of inflammation; however, its role in the current situation remains undefined. Counseling by pharmacists may improve the current situation significantly.

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