Cardiac safety analysis of first-line chemotherapy drug pegylated liposomal doxorubicin in ovarian cancer

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Abstract
Pegylated liposomal doxorubicin (PLD) is a nano-doxorubicin anticancer agent. It was used as early as 2014 to treat ovarian and breast cancer, multiple myeloma and Kaposi's sarcoma. The 2018 National Comprehensive Cancer Network guidelines listed PLD as first-line chemotherapy for ovarian cancer. PLD has significant anticancer efficacy and good tolerance. Although PLD significantly reduces the cardiotoxicity of conventional doxorubicin, its cumulative-dose cardiotoxicity remains a clinical concern. This study summarizes the high-risk factors for PLD-induced cardiotoxicity, clinical dose thresholds, and cardiac function testing modalities. For patients with advanced, refractory, and recurrent malignant tumors, the use of PLD is still one of the most effective strategies in the absence of evidence of high risk such as cardiac dysfunction, and the lifetime treatment dose should be unlimited. Of course, they should also be comprehensively evaluated in combination with the high-risk factors of the patients themselves and indicators of cardiac function. This review can help guide better clinical use of PLD.

Keywords: Pegylated liposomal doxorubicin, Cardiotoxicity, High-risk factors, Cardiac function test, Ovarian cancer

Introduction
Doxorubicin (Dox) is an anthracycline compound with the molecular formula of C_{27}H_{29}NO_{11}. Its chemical structure is shown in Fig. 1. It acts as a topoisomerase I inhibitor, can effectively inhibit the synthesis of DNA and RNA in tumor cells, and plays a cytotoxic role. In 1964, the Food and Drug Administration (FDA) clinically approved Dox for the treatment of a variety of cancers, such as ovarian cancer, thyroid cancer, stomach cancer, breast cancer, lymphoma, multiple myeloma, and sarcoma [1]. However, doxorubicin is reduced to semiquinone in the body; after the oxidation reaction, it can lead to the generation of free radicals and attack the myocardial mitochondrial membrane. Given that the myocardial ability to scavenge free radicals is low, myocardial toxicity occurs. The affinity of Dox to the myocardium is significantly higher than that to other tissues in the body, which makes the myocardium more vulnerable to Dox damage. Cardiotoxicity can manifest as acute or subacute damage immediately after treatment, or delayed cardiomyopathy after several years. Therefore, the mortality caused by Dox dose-dependent severe heart failure can be as high as 20%, which limits its clinical application [2].

Since 1971, when Gregoriadis and Rymen first reported the use of liposomes as drug carriers, liposomes have been used as effective carriers of anthracycline drugs. Liposomes are double-layer phospholipid membrane vesicles with similar biomembrane structures. Most of the liposomes cannot penetrate tissue capillaries, and the increased permeability of tumor tissue capillaries increases the local enrichment of drugs, thereby increasing their antitumor effect. Since 1995, liposome
doxorubicin (Doxil), the first nano-particle–based antitu-
mor drug approved by the FDA, has widely been used in
the treatment of various tumors [3]. However, the clinical
application of Doxil is also limited due to its poor struc-
tural stability, drug leakage, short storage life, poor tissue
targeting, and easy clearance by the body.

PEGylated liposomal doxorubicin (PLD) is a new
type that wraps macromolecular substance Polyeth-
ylene glycol (PEG) on the surface of Doxil. PEG mac-
romolecule can be covalently connected to the amino
group of distearoyl phosphatidyl-ethanolamine (DSPE)
(Fig. 2). It is composed of 45 ethylene glycol monomers
and binds between 135 and 180 water molecules. This
highly mobile and highly hydrated PEG macromolecule
increases the stability of the Doxil spatial structure [4]. A
previous study has shown that PLD accumulates in the
liver, spleen, and tumor, but not in the heart tissue [5].
Dox in the heart tissue was only 38.1%. The release rate
of Dox in the heart was much slower than that in other
tissues, which could effectively reduce the cardiotoxicity
of Dox. Therefore, PLD is widely used to treat metastatic
breast cancer, ovarian cancer, progressive myeloma,
refractory AIDS-related Kaposis sarcoma (KS), and other
solid tumors [6]. Although PLD can reduce the cardio-
toxicity of Dox, its impact on the heart has not been fully
revealed, and is still the focus of clinical attention.

**Strengths and limitations of pegylated liposomal
doxorubicin in the treatment of ovarian cancer**

The 2017 National comprehensive cancer network
(NCCN) Guidelines recommended that carboplatin
combined with PLD be added as one of the initial chemo-
therapy regimens for ovarian cancer. PLD plus carboplatin
produced a better Progression-free survival (PFS)
than standard-regimen Paclitaxel plus carboplatin and
was well tolerated. Clinical study supported the con-
tinued use of PLD plus carboplatin as first-line chemo-
therapy for platinum-sensitive recurrent ovarian cancer,
and recommend PLD at 30 mg/m$^2$ every 4 weeks can be
used as the initial dose. As a single-agent therapy, PLD
manifested survival similar to other agents and was well
tolerated. PLD monotherapy as first-line chemotherapy
for platinum-resistant or -refractory recurrent ovarian
cancer, and clinical recommend using PLD at a dose of
40 mg/m$^2$ every 4 weeks as the initial dose [7–9].

The most concerning potential side effect of Dox and
PLD is often cited as congestive heart failure (CHF), and
doxorubicin is in fact closely associated with CHF. PLD's
parent drug is Dox, but PLD can effectively reduce car-
diac toxicity.

**Pegylated liposomal doxorubicin reduces doxorubicin
cardiotoxicity**

The mechanism of cardiac injury is related to the produc-
tion of free radicals. Free radicals induce peroxidation
of muscle cell membrane, mitochondrial damage, and sub-
sequent calcium inflow into cells, and the cytoplasm of
isolated cells in myocardium becomes vacuolized. With
the increase of Dox cumulative dose, more cells are
involved, eventually leading to chronic and irreversible
dilated cardiomyopathy and CHF.

A previous study found that the cardiotoxicity of Dox
was related to the peak concentration of plasma Free-
Dox [10]. The mechanism by which PLD reduces car-
diac toxicity may be that PLD does not enter into tight
capillary junctions like gastrointestinal tract and heart
because of the size of liposomes[8], which results in less
distribution of Dox in the myocardium [11]. Second,
PEG macromolecule reduces the interaction between
liposomes and blood component including opsonins and
macrophages, maintains the liposome shape before Dox
enters the tumor, and prolongs the circulation time of 
Dox. PEGylated coating of PLD forms a hydrophilic bar-
rier protecting the liposomes from reticuloendothelial 
system detection and prolong the half-life of drugs in vivo 
[12]. Therefore, PLD leaves blood vessels much slower 
than Dox [13–, 14–16]. The prolongation of drug half-life 
significantly limits the peak value of Dox exposure to the 
myocardium, thereby reducing cardiac toxicity. Second, 
the release rate of PLD is also closely related to the gradi-
ent of ammonium sulfate in the tissue microenvironment 
[17]. In an additional study, it was demonstrated that 
PLD made with ammonium-methane sulfonate exhibit a 
much lower Hand and Foot syndrome (HFS) [18]. This 
will likely be the next research focus.

Clinical cumulative dose threshold of pegylated liposomal 
doxorubicin

Dox resistance is multifactorial and involves a variety of 
cellular mechanisms, but at least some of these resistance 
mechanisms are reversible [19]. PLD has been proven 
to overcome P-glycoprotein (Pgp) mediated multidrug 
resistance [20]. Therefore, PLD may be an effective treat-
ment option for recurrent cancer [21, 22]. For metastatic 
breast cancer, PLD can be used for re-treatment without 
cumulative toxicity [23]. PLD is the first-line chemother-
apy drug for advanced KS. Due to the limited substitu-
tion therapy for KS, long-term multi-course PLD treatment is 
sometimes required. When the cumulative dose exceeds 
500 mg/m², there is little evidence to support stopping 
PLD treatment for patients with refractory HIV-related 
KS. Similar to conventional Dox, PLD cumulative dosing 
should not exceed 550 mg/m² because of the risk of CHF 
[5]. Therefore, further studies are needed to determine 
the threshold of cumulative-dose cardiotoxicity of PLD 
in the treatment of advanced, refractory, and recurrent 
malignant tumors [24].

A randomized clinical trial reported that when the 
cumulative PLD dose reached 1061 mg/m², less than 2% 
of patients developed nonfatal heart failure [25]. Other 
studies have found that patients with recurrent ovar-
ian cancer who received a PLD cumulative dose of up 
to 2877 mg/m² did not have a significant decline in car-
diac function [26, 27]. Roswell Park Cancer Institute 
retrospectively studied ovarian cancer patients who had 
received a cumulative dose of PLD 6400 mg/m² with-
out interruption or discontinuation of treatment due to 
cardiotoxicity [28]. It has been confirmed that patients 
receiving PLD > 500 mg/m² or PLD combined with previ-
ous Dox have no PLD-related heart failure after 10 years 
of follow-up [29].

When the dose exceeded 1110 mg/m², the left ven-
tricular ejection fraction (LVEF) decreased by more 
than 10% in 3.5% (5 cases) of patients; two of these 
cases were previously diagnosed as CHF, and a cumu-
lative dose threshold of PLD 1000 mg/m² was recom-
mended for people at high risk [27]. Andreopoulos et al. 
studied PLD combined with other chemotherapy drugs. 
Among patients who had been treated for more than a 
year and whose cumulative dose reached 2460 mg/m², 
only one patient developed transient heart failure when 
neutropenic sepsis related to topotecan administration 
occurring 10 months after stopping PLD [30]. Therefore, 
for people at high risk of cardiotoxicity, PLD cumula-
tive dose should be reduced and cardiac function testing 
should be performed.

For patients with advanced, refractory, and recurrent 
malignant tumors, the use of PLD is still one of the most 
effective strategies in the absence of evidence of high risk 
such as cardiac dysfunction [23], and the lifetime treat-
ment dose should be unlimited [25] (Table 1).

High risk population for pegylated liposomal doxorubicin 
induced cardiotoxicity

High interindividual variability based on age and sex and 
cardiotoxicity related to plasma pharmacokinetics are 
unpredictable [39]. For high-risk groups (previous chest 
wall mediastinal radiotherapy history, elderly women, 
previous diagnosis of congestive heart failure, subjective 
symptoms, or clinical evidence of cardiotoxicity), cardiac 
function testing and reduction of cumulative dose are 
necessary.

Elderly individuals

For elderly patients, the use of PLD adjuvant chemother-
apy has attracted attention [31]. It has been shown that 
during PLD treatment, three patients had cardiac symp-
toms that may be related to PLD or aggravated by PLD 
[32]. These patients were more than 65 years old. Because 
elderly patients often have chronic complications, there 
are a variety of cardiac risk factors, such as uncontrolled 
high blood pressure, history of myocardial infarction, 
aortic stenosis, and arrhythmia, so older age is one of the 
high-risk factors of PLD dose [40].

Women

Male patients with solid tumors or KS show twofold 
accelerated plasma clearance compared with women of 
all ages [41]. In a clinical study of female patients with 
advanced breast cancer, patients who received PLD at a 
cumulative dose of 450–550 mg/m² had an 11% risk of 
cardiotoxicity. For ovarian cancer, the high cumulative 
dose of PLD exceeds the total lifetime cumulative dose of 
550 mg/m² initially recommended by FDA, but there is a 
lack of evidence to support the standard practice guide-
lines for these patients [12].
Compared with the general population, the cardiovascular mortality of female patients with breast cancer is increased, and the risk is about twice as high when considering age, menopausal status, and other typical risks [15]. The increased cardiovascular incidence rate in female patients with breast cancer is due to the frequent occurrence of adverse classic risk factors that are usually not optimally controlled (such as smoking, low physical activity, high body mass index, dyslipidemia) and the adverse effects of cancer treatment [42]. If women have other risk factors, such as diabetes or hypertension, Dox therapy brings a higher risk of cardiovascular death after breast cancer [43, 44]. Although this source of variability is not considered in the current PLD administration guidelines, it is necessary to be cautious in the clinical application [6].

| Study                           | Intervention | Type of trial                                      | Patient characteristics | Outcomes                               |
|--------------------------------|--------------|---------------------------------------------------|-------------------------|----------------------------------------|
| Zhen Yuan 2021 [9]             | PLD 40 mg/m² q4wks 6 cycles | open-label, single-arm and multicenter prospective clinical trial | ovarian cancer          | ORR, DCR, AEs, QOL                     |
| ALEX 2015 [26]                 | PLD 40 mg/m² q4wks longer than 1 year | retrospective chart clinical trial                  | recurrent ovarian, tubal and peritoneal carcinoma | PFS, OS, Cardiac Toxicity             |
| Sarah E 2013 [27]              | PLD 40 mg/m² q4wks adjustments for toxicity consisted of either dose reduction or treatment delay | retrospective chart clinical trial                  | recurrent or refractory ovarian cancer, or endometrial cancer, primary peritoneal cancer, and fallopian tube cancer | Cardiac Toxicity                     |
| Joshua P 2010 [28]             | PLD 30 or 40 mg/m² q4wks adjustments for toxicity consisted of either dose reduction or treatment delay | retrospective chart clinical trial                  | ovarian cancer, primary peritoneal, endometrial, fallopian, tube, cervix and vulva cancer | Cardiac Toxicity                     |
| E. Andreopoulou 2008 [30]      | PLD 30 or 40 mg/m² q4-8wks adjustments for toxicity consisted of either dose reduction or treatment delay | retrospective chart clinical trial                  | recurrent ovarian cancer, fallopian tube cancer | Cardiac Toxicity                     |
| M. E. R. O’Brien 2004 [31]     | PLD 50 mg/m² q4wks doxorubicin 60 mg/m² q3wks | phase III randomized multicenter, open-label trial | women with metastatic breast cancer | PFS, OS, Cardiac Toxicity             |
| Denise Uyar 2004 [32]          | PLD 20 or 40 mg/m² q4-6wks ≥ 6 cycles | retrospective chart clinical trial                  | ovarian cancer, primary peritoneal and endometrial cancer | Cardiac Toxicity                     |
| Sandrine Faivre 2004 [33]      | PLD 35 mg/m² q3wks PLD 45 mg/m² q3wks | phase I–II randomized multicenter, open-label trial | recurrent squamous cell carcinoma of the head and neck | ORR, Toxicity                         |
| C.L. Kushnir 2015 [34]         | PLD cumulative doses of 300 mg/m² (range 60–1420 mg/m²) | retrospective chart clinical trial                  | ovarian cancer, primary peritoneal, Fallopian tube, endometrium, cervix, GYN origin, ovary and endometrium, Vaginal cancer | Cardiac Toxicity                     |
| Keith M 2017 [35]              | cumulative doxorubicin > 450 mg/m² (free doxorubicin combined with PLD),25% patients > 1000 mg/m² | retrospective chart clinical trial                  | advanced malignancies | Cardiac Toxicity                     |
| G. Berry 1998 [36]             | cumulative PLD (20 mg/m² q2wks) of 44G—840 mg/m² cumulative doxorubicin (20 mg/m² q2wks) of 174–671 mg/m² | retrospective chart clinical trial                  | AIDS Kaposi’s sarcoma | Cardiac Toxicity                     |
| Cardiac Toxicity 2004 [37]     | cumulative doxorubicin dose of > 550 mg/m² (including PLD) or > 400 mg/m² of PLD alone | retrospective chart clinical trial                  | advanced malignancies | Cardiac Toxicity                     |
| Sarah E 2013 [38]              | PLD median dose of 200 mg/m² (range 40–1775 mg/m²) | retrospective chart clinical trial                  | ovarian cancer, endometrial and other cancer | Cardiac Toxicity                     |

ORR Objective response rate, DCR Disease control rate, AEs Adverse events, QOL Quality of life, PFS Progression-free survival, OS Overall survival, AIDS Acquired immune deficiency syndrome
Child
Children may be more susceptible to the cardiac effects of anthracyclines compared with adults [45]. Genetic variations seem to be associated with the development of Dox-induced cardiotoxicity in children, so the current PLD research findings may not be applicable to the treatment of children with cancer [46].

Previous heart disease and chest wall/mediastinal radiotherapy history
In a study on PLD treatment for women with recurrent ovarian or peritoneal cancer, the cumulative dose of PLD was more than 550 mg/m², and the median follow-up time was 20 months. Among them, 53 patients had obvious preexisting cardiac risk factors (previous cardiomyopathy, previous chest wall/mediastinal radiotherapy) and received initial cardiac assessment or monitoring. Only three patients (1.6%) developed CHF that may be related to PLD treatment.

Doxil might protractedly release doxorubicin in interstitial areas as liposomes diffuse slowly into the tumor tissue [47]. Prior high doses of radiotherapy might facilitate this process since late radiation induced tissue modifications, including fibrosis, would establish intratumoural conditions that rapidly breakdown the extravasated liposomes, facilitating doxorubicin radiation recall effects, slowing down healing processes, and inducing tumor necrosis [48]. Therefore, this drug needs to be used carefully for tumors relapsing in irradiated areas [33]. In radiotherapy for breast cancer, left breast radiotherapy is also associated with a higher risk of cardiovascular death and myocardial infarction death than right breast radiotherapy [49]. For patients undergoing concurrent radiotherapy and chemotherapy, the clinical application of PLD requires paying attention to these related risks.

Doxorubicin in childhood
Dox induced cardiotoxicity can be delayed, especially in cancer survivors treated during childhood. Among these cancer survivors, the incidence rate of heart failure and other heart diseases is much higher than the incidence rate in the general population [34]. In these patients, cardiac function should be monitored if PLD treatment is needed again in adulthood.

Cardiac function monitoring method

Left ventricular ejection fraction
FDA recommends routine assessment of LVEF by multigated radionuclide angiography (MUGA) or echocardiography before, during, and after PLD treatment [12]. The decrease in LVEF is regarded as a biomarker that is related to heart failure or can predict the development of heart failure [50]. Of note, 11% is the minimum change in LVEF, and the recognizable confidence is 95% [51]. The most sensitive cardiac function monitoring method is continuous measurement of LVEF. Gill et al. suggested that baseline LVEF may be sufficient to determine the overall cardiac risk during PLD treatment [23]. If the baseline LVEF is less than 30%, the use of such drugs is not recommended. When the baseline LVEF is above 30% but below 50%, patients can still receive treatment, but the LVEF needs to be measured repeatedly before each course of treatment. For patients with baseline LVEF above 50%, routine cardiac testing can be ignored [34]. However, some scholars believe that although LVEF is widely used to monitor the cardiotoxicity of Dox, and there are various guidelines and recommendations, the use of LVEF is not without shortcomings [35]. Clinically, there are also heart failure patients with normal ejection fraction (LVEF > 50%). Because the significant decrease in LVEF does not necessarily occur gradually, but may occur suddenly. In normal subjects, LVEF may change moderately every day depending on hydration status. Transient changes in LVEF that are not related to Dox are not uncommon in clinical practice, and may lead to premature cessation of treatment before reaching the maximum recommended cumulative dose. Therefore, the utility of LVEF changes in predicting Dox-induced heart failure has not been fully demonstrated, and it may not be the best objective indicator [35].

Doppler-based myocardial deformation imaging
Early cardiac function changes induced by chemotherapy are subtle, and LVEF is too insensitive to detect subtle changes in cardiac function [52]. Velocity, strain, and strain rate measurements based on Doppler myocardial imaging have been shown to be sensitive in quantifying cardiac dysfunction in other situations. Compared with conventional echocardiography and myocardial velocity measurement, myocardial deformation parameters (S and SR) allow for the detection of subtle changes in left ventricular longitudinal and radial function after six cycles of PLD. We recommend Doppler-based myocardial deformation imaging (DMI) for monitoring cardiac function during chemotherapy [53–56].

Endomyocardial biopsy
Berry et al. consider endomyocardial biopsy (EMB) as the gold standard [36]. Biopsy grade is predictive of the rate of progression of cardiotoxicity and is considered the most sensitive indicator of conventional doxorubicin-induced cardiotoxicity. A study confirmed that the Billingham score of all patients with HIV-related KS, breast cancer, and ovarian cancer with PLD > 500 mg/m² (500–1485 mg/m²) was lower than 1.5, indicating that none of the patients had significant histological myocardial
Conclusions

Most patients receiving PLD treatment suffer from advanced, refractory, or recurrent malignant tumors. Quality of life and symptom relief are their main concerns [38]. The commonly used cardiac function testing methods in clinical practice have advantages and disadvantages. It is suggested that they can only be used for auxiliary evaluation, and they cannot directly predict the cardiac toxicity of PLD treatment. Overall, PLD cardiac safety is good and there is no absolute upper limit for clinical cumulative dose. They also should be comprehensively evaluated in combination with the high-risk factors of the patients themselves and the variability between individuals.

Abbreviations

AIDS: Acquired Immune Deficiency Syndrome; AEs: Adverse events; CHF: Congestive heart failure; Dox: Doxorubicin; DCR: Disease control rate; DSPE: Distearoyl-phosphatidylethanolamine; DMI: Doppler based myocardial deformation imaging; EMB: Endomyocardial biopsy; FDA: Food and Drug Administration; HFS: Hand and Foot syndrome; KS: Kaposis’s sarcoma; LVEF: Left ventricular ejection fraction; Doxil: Liposome doxorubicin; MUGA: Multi gated radionuclide angiography; NCCN: National comprehensive cancer network; ORR: Objective response rate; OS: Overall survival; PLD: Pegylated liposomal doxorubicin; PFS: Progression free survival; Pgp: P-glycoprotein; PEG: Polyethylene glycol; QOL: Quality of life.

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Authors’ contributions

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Competing interests

All the authors declare no competing interests.

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