Monitoring long-term treatment with pegylated liposomal doxorubicin: how important is intensive cardiac follow-up?

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Pegylated liposomal doxorubicin (PLD; Doxil or Caelyx) has been shown to be as effective as conventional doxorubicin, and to have a significantly better cardiac safety profile. The aim of this study was to assess the safety of delivering doses exceeding 700 mg/m^2 of PLD to patients with solid tumors. A review of the medical records of 149 patients with a variety of solid tumors treated with PLD was performed. The findings in 12 patients who had reached or exceeded cumulative doses of 700 mg/m^2 (median = 1.071 mg/m^2, range 712–1856 mg/m^2) were reviewed. Changes in left ventricular ejection fraction (LVEF), and in clinical cardiac status were analyzed. The median age of the patients was 53.9 years and the median follow-up from the start of PLD treatment was 44.6 months. None of the 12 patients had clinical congestive heart failure secondary to cardiomyopathy. Seven of the 12 patients underwent further assessment of LVEF by echocardiography or multiple gated acquisition scan, which revealed a stable or improved ejection fraction. PLD is cardiac safe for long-term treatment of metastatic solid tumors. Its maximal cumulative dose remains undefined. Frequent determinations of LVEF, as routinely done for other anthracyclines, do not appear to have any clinical value in patient follow-up. In metastatic patients with no evidence of cardiac risk factors, it may be sufficient to measure LVEF at baseline. ***Anti-Cancer Drugs*** **21:868–871 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Doxorubicin has been shown to be effective in the treatment of a wide variety of cancers. The usefulness of conventional doxorubicin is limited, however, by cardiotoxicity in the form of cumulative dose-related cardiomyopathy [1,2]. In severe cases, this can lead to congestive heart failure (CHF) and even death. Although in the majority of instances cardiotoxicity tends to appear late in the course of treatment, after cumulative doses in excess of 450–500 mg/m^2, or just after the cessation of treatment, in some cases it may only become apparent many years after therapy has ceased, under situations of cardiac stress. The correlation of doxorubicin treatment with cardiomyopathy and CHF became firmly established in the clinic by two studies published in 1979 [3,4]. In one of these studies, Von Hoff *et al.* [3] examined the records of 4018 doxorubicin-treated patients and established that there was a continuum of increasing risk of doxorubicin-induced CHF as the cumulative amount of administered drug increased. The probability of developing CHF at cumulative doses of 400, 550, and 700 mg/m^2 was 3, 7, and 18%, respectively. However, for >60-year-old patients, the risk rose to 4.6, 13.9, and 43.5%, respectively, for the same three cumulative dose levels given at the standard 3-weekly schedule [3].

A more recent report in 2003 involving 630 patients treated with doxorubicin alone in three controlled trials confirmed the earlier findings and estimated that as many as 26% of patients receiving a cumulative doxorubicin dose of 550 mg/m^2 and 48% of those receiving a cumulative dose of 700 mg/m^2 would develop doxorubicin-related CHF, whereas the incidence of CHF was only 5% at the cumulative doses of up to 400 mg/m^2 [5]. Age was also identified in this study as an important risk factor for doxorubicin-related CHF after a cumulative dose of 400 mg/m^2, with older patients (age >65 years) showing a greater incidence of CHF compared with younger patients [5].

Mild levels of cardiac damage may not be recognized clinically, but become evident when cardiac function, and particularly left ventricular ejection fraction (LVEF) is monitored before the commencement of therapy, and thereafter at regular intervals throughout, and after the treatment period. LVEF is usually monitored using either echocardiography or multiple gated acquisition (MUGA) radioisotopic scans [6]. Although at first sight this may appear to be an ideal strategy for the early detection of cardiotoxicity in these patients, transient changes in LVEF not related to anthracycline administration occur not infrequently, and may lead to the premature cessation of therapy before the maximum recommended cumulative dose has been reached [7].

Various strategies have been used in an attempt to circumvent the cardiotoxicity of the conventional drug. These include alteration of the dosage schedule to modify

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the pharmacokinetics, particularly the peak plasma concentration; concurrent use of cardioprotective agents such as dexrazoxane; and the use of liposomal delivery systems [8]. Pegylated liposomal doxorubicin (PLD; known under the commercial names of Doxil or Caelyx) has been shown in a number of studies to be as effective as conventional doxorubicin, and to have a significantly better cardiac safety profile [9–12], thus enabling higher cumulative doses to be administered. These studies all used LVEF as an objective measure of cardiac function. We wondered whether intense serial measurement of LVEF was indicated in patients receiving PLD who did not exhibit certain well-recognized risk factors, and to help us resolve this question, we have carried out a retrospective survey of patients in the unit who have been treated with high cumulative doses of PLD over the past 10 years.

Materials and methods

A retrospective analysis was carried out on all patients who had received PLD in the Shaare Zedek Oncology Unit for the treatment of a solid tumor, over the past 10 years. From this group, the cohort who had received cumulative doses in excess of 700 mg/m^2 was identified. This comprised 12 patients (11 female and 1 male; Table 1). The median age was 53.9 years (range 44–71 years). There were five patients with ovarian cancer, two with breast cancer, four with soft tissue sarcomas and one patient with squamous cell carcinoma of the tongue. All diagnoses were biopsy-proven, and all patients had metastatic disease. Three patients had earlier received conventional doxorubicin-based chemotherapy for the treatment of their disease: one patient with sarcoma had received 240 mg/m^2 for an episode of breast cancer 10 years earlier; one patient with breast cancer had started treatment with conventional doxorubicin and after a cumulative dose of 120 mg/m^2 was switched directly to PLD treatment. The patient with squamous cell carcinoma of the tongue had also received 240 mg/m^2 of the conventional preparation earlier before direct change to PLD therapy.

The initial dose of PLD per course was 40–60 mg/m^2 every 4 weeks with dose reduction to 40–45 mg/m^2 in the second or third cycle. This lower dose was then maintained for the duration of treatment with PLD. In every case the PLD was administered by intravenous infusion over a period of 1–2 h.

Ten patients had a baseline assessment of LVEF; in five cases this was measured echocardiographically and in five cases by MUGA. Seven of these patients had a further assessment of LVEF carried out after the patient had received a cumulative dose of 700 mg/m^2 or more. This was measured by echocardiography in five cases and by MUGA in two cases.

Results

The median cumulative dose of PLD was 1071 mg/m^2 (range 712–1856 mg/m^2). Six patients received the cumulative doses in excess of 1000 mg/m^2: three in excess of 800 mg/m^2 and three in excess of 700 mg/m^2. The duration of clinical follow-up from the start of treatment with PLD ranged from 24 to 101 months. Eight patients died without clinical symptoms of heart disease; of these, four did not undergo LVEF monitoring.

No clinical evidence of cardiotoxicity was observed in any patient throughout the course of PLD treatment, and in the seven patients in whom both baseline and follow-up LVEF readings were obtained, these improved over the treatment period in four of the patients, decreased by 1% in a fifth patient and were stable in the remaining two (Table 1).

Discussion

Cumulative dose-related cardiotoxicity is the most serious potential adverse effect associated with conventional doxorubicin treatment [1]. Histologically, the first evidence of cardiac damage is recognizable as the presence of cytoplasmic vacuolation in isolated cells throughout the myocardium [13]. More cells become involved with increase in cumulative dose, leading ultimately, in severe cases, to a chronic, irreversible dilated cardiomyopathy and CHF, which in some cases may be fatal. The mechanism of cardiac damage is believed to be related to the production of free radicals that induce peroxidation of myocyte membranes, mitochondrial damage, and the subsequent influx of calcium into the cells [14].

Table 1 Summary of patients data

	Age, sex	Diagnosis	Cumulative dose, mg/m^2	Follow-up	EF before PLD	EF follow-up	Previous doxorubicin	Risk factors
1	44, Female	Breast	1856	101 m	63% (E)	64% (E)	–	
2	56, Female	Sarcoma	1480	41 m, D	65% (M)	71% (M)	–	–
3	34, Female	Ovary	1442	44 m	60% (M)	72% (E)	–	–
4	58, Female	Ovary	1060	41 m, D	61% (M)	65% (E)	–	DM, HTN
5	55, Female	Sarcoma	1045	31 m, D	65% (E)		240 mg/m^2	RTx (Lt breast)
6	60, Female	Ovary	1036	51, D			–	DM, HTN
7	71, Female	Sarcoma	980	49 m, D	63% (E)	64% (M)	–	Age
8	61, Female	Breast	875	52 m D	81% (M)		120 mg/m^2	RTx (Lt breast)
9	49, Male	SCC of tongue	860	38 m	50% (E)	49% (E)	240 mg/m^2	–
10	54, Female	Ovary	777	33, D			–	–
11	57, Female	Ovary	727	30 m, D	62% (M)		–	–
12	48, Female	Sarcoma	712	24 m	65% (E)	65% (E)	–	–

D, death; DM, diabetes mellitus; E, echocardiography; EF, ejection fraction; HTN, hypertension; Lt, left; M, multiple gated acquisition; PLD, pegylated liposomal doxorubicin; RTx, radiotherapy; SCC squamous cell carcinoma.

Various factors have been recognized which can increase the likelihood of cardiotoxicity, and these include advanced age, hypertension or other pre-existing cardiac conditions, earlier radiotherapy to the mediastinum or left chest wall, earlier adjuvant anthracycline therapy, and earlier or concurrent administration of other chemotherapeutic agents such as cyclophosphamide or trastuzumab.

The reduced cardiotoxicity of PLD compared with that of conventional doxorubicin has been shown in a number of studies. In a prospective study, Gabizon *et al.* [15] performed endomyocardial biopsies in eight patients with advanced malignancies after a median PLD dose of 707.5 mg/m^2 and a median total anthracycline exposure of 908.5 mg/m^2. Median biopsy score (Billingham scale) was 0.75 (range 0–1.5). The investigators concluded that the administration of doxorubicin as PLD minimizes its cardiotoxic potential, even at doses in excess of the recommended lifetime cumulative dose of 450–550 mg/m^2.

A retrospective analysis of phase I and phase II studies involving 237 patients with solid tumors treated with PLD was carried out by Safra *et al.* [10]. LVEF was assessed with MUGA scans at baseline and at prescribed intervals throughout the treatment period. Forty-two patients had received $\geq$ 500 mg/m^2 (range 500–1500 mg/m^2). None of these patients had clinical evidence of CHF secondary to cardiomyopathy. Posttreatment scans were available for 41 of these patients. In only five patients (three of whom had received doxorubicin earlier), a 10% reduction in LVEF was noted. The investigators concluded that cumulative doses of PLD in excess of 500 mg/m^2 were associated with a substantially reduced risk of cardiomyopathy than is the case with the conventional form of the drug [10].

Andreopoulou *et al.* treated 16 patients with recurrent ovarian or fallopian tube cancer with PLD for more than 1 year [8]. Baseline LVEF measurements were obtained using MUGA scans and further assessment of LVEF were to be made after every 300 mg/m^2 (approximately annually) and at completion of treatment, using either echocardiography or MUGA. Fourteen of the patients received cumulative doses in excess of 700 mg/m^2 (range 760–2125 mg/m^2) and 11 of these had an assessment of LVEF at the conclusion of treatment. There was no evidence of a confirmed decline in LVEF in these patients, and the investigators stated that the fear of clinical cardiac problems is unwarranted if the patient's medical status is stable and they have not been exposed to anthracyclines earlier [8].

O'Brien *et al.* [12] showed that PLD has equivalent efficacy to doxorubicin with significantly less cardiotoxicity, when used as first-line therapy in the treatment of women with metastatic breast cancer. The risk of developing cardiotoxicity was significantly higher in patients receiving doxorubicin than in those receiving PLD with a hazard ratio of 3.16 for comparison of cumulative anthracycline dose at the first, protocol-specified, cardiac event. At cumulative doses at or above 450 mg/m^2, a seven-fold greater mean percentage decrease in LVEF was observed with doxorubicin compared with PLD (mean percentage change from baseline in LVEF: –17.2 versus –2.3% in doxorubicin-treated and PLD-treated patients, respectively).

In a phase III study, Orlowski *et al.* [16] showed that the combination of PLD with the proteasome inhibitor bortezomib is superior to bortezomib monotherapy for the treatment of patients with relapsed or refractory multiple myeloma. Of the patients treated with PLD and bortezomib, symptomatic cardiac events were reported in 7% compared with 5% in those treated with bortezomib alone. These comprised CHF (3 vs. 3%), symptomatic arrhythmia (3 vs. 1%), ischemic coronary disease (1 vs. 1%) and other cardiac events (2 vs. 1%). In some instances the patients experienced more than one type of cardiac event.

This study has obvious limitations and cannot provide guidelines for the clinical cardiac follow-up of patients receiving PLD for the treatment of solid tumors. When viewed in the context of our gradual learning curve on the cardiac safety of PLD, however, it would appear that the frequent determination of LVEF, which is currently common practice for patients receiving conventional doxorubicin, is unwarranted in patients receiving PLD. In patients with metastatic disease and no evidence of cardiac risk factors, it may be sufficient to measure LVEF at baseline, and thereafter only after cumulative doses $\geq$ 500–700 mg/m^2, or as indicated clinically. If PLD is to be used as adjuvant therapy, it may only be necessary to record a baseline LVEF as the total cumulative dose of PLD in these circumstances is usually of the order of 300 mg/m^2. After adjuvant therapy, however, the life expectancy of the patient may extend for many decades, and it is known that the late cardiotoxicity of conventional doxorubicin may only become apparent many years after the cessation of therapy. It is therefore clear that a definitive algorithm for the cardiac monitoring in all patients receiving PLD will need to take all these factors into consideration.

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