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ORIGINAL ARTICLE

Cardiac safety profile of patients receiving high cumulative doses of pegylated-liposomal doxorubicin: use of left ventricular ejection fraction is of unproven value

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Abstract
Purpose One of the great conundrums for both oncologists and cardiologists is how to best monitor the potential and actual cardiotoxicity of doxorubicin. Pegylated-liposomal doxorubicin (PLD) has a safer cardiotoxicity profile than bolus administration of doxorubicin. Although ejection fraction (EF) is commonly performed to monitor doxorubicin-induced cardiotoxicity, evidence for its predictive utility is limited. We examined the incidence of doxorubicin-induced heart failure (HF) in patients who received a large cumulative dose of doxorubicin as PLD and its relation to EF and HF.
Methods A retrospective chart review of patients who received a large cumulative dose of PLD, sometimes after previous free doxorubicin treatment, was performed to examine the incidence of doxorubicin-induced heart failure (HF) and its relation to EF and development of HF.
Results No definite doxorubicin-induced clinical HF was observed among 56 patients (median age 54; 15–93) who received a cumulative doxorubicin dose (free + PLD) of >450 mg/m^2. Of these, 49 received >500 mg/m^2, 28 > 700 mg/m^2, 19 > 800 mg/m^2, 14 > 1000 mg/m^2, and 5 > 1400 mg/m^2. The EF varied greatly over time in some patients treated with PLD in the absence of symptoms or signs of heart failure, and was not particularly useful in making decisions regarding further dosing.
Conclusions Pegylated-liposomal doxorubicin was associated with a low risk of doxorubicin-induced HF in a retrospective cohort of patients receiving large cumulative doses of doxorubicin and long-term follow-up. EF did not predict doxorubicin-induced cardiotoxicity in our cohort of adult patients receiving PLD. Given the lack of prognostic clarity regarding modest EF changes, regular EF monitoring may not be warranted, at least when PLD is used in adults. Modest changes in EF should probably not be used to limit a patient's access to PLD, but may warrant cardiology consultation for long-term follow-up after completion of therapy.

Keywords Anthracycline · Cardiotoxicity · Cardio-oncology · Ejection fraction · Heart failure · Pegylated-liposomal doxorubicin

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Introduction

One of the great conundrums for both oncologists and cardiologists is how to best monitor the potential and actual cardiotoxicity of doxorubicin. Despite its efficacy, the use of doxorubicin is limited by its dose-related cardiotoxicity, which may manifest as a reduction in ejection fraction (EF) and/or development of clinical (HF). While several risk factors for doxorubicin-induced heart failure (HF) have been

reported, the cumulative dose administered appears to be the most important one [1]. Retrospective studies have found a ~7.5% incidence of clinical HF at a cumulative dose of 550 mg/m^2 of free doxorubicin [1], and prospective trials have found even higher rates [2]. In one large series, the incidence of HF rose to ~20–30% at 700 mg/m^2, reaching ~50% in the setting of prior cardiovascular disease, and to ~50% at 1000 mg/m^2 with no prior cardiovascular disease [1]. However, the diagnosis of HF is typically a clinical exercise (i.e., bedside) and is subject to error [3].

The cardiotoxicity of doxorubicin appears to correlate with peak plasma levels and total cumulative dose [4]. A weekly schedule of administration is associated with a lower incidence of HF than an every 3-week schedule [1], and continuous intravenous infusion (CIVI) of doxorubicin is associated with less cardiotoxicity than bolus administration [4–10].

Pegylated-liposomal doxorubicin (PLD) is a liposomal formulation of doxorubicin in which the doxorubicin is contained in liposomes that are coated with methoxypoly (ethylene glycol). The methoxypoly (ethylene glycol) coating results in less uptake by the reticuloendothelial system and a much longer half-life in blood than non-pegylated liposomes [11–13]. The toxicity profile of PLD is more similar to that of CIVI doxorubicin than bolus administration of doxorubicin [9–11]. The long intravascular half-life of PLD markedly limits peak doxorubicin exposure to the myocardium [11–13]. Animal studies found less histologic evidence of myocardial damage with PLD relative to free doxorubicin [14, 15], and human studies suggest the same results [11, 13, 16–20]. Studies in Kaposi sarcoma found lower endomyocardial biopsy scores in patients treated with PLD (near normal scores) as compared with free doxorubicin [16]. Two studies in breast cancer found PLD had less cardiotoxicity than doxorubicin [17, 20]. Retrospective studies of PLD treatment found no clinical HF attributed to PLD among 42 patients who received ≥500 mg/m^2, 116 patients who received ≥400 mg/m^2, or 22 patients who received >550 mg/m^2 [21–23]. Phase II trials of PLD patients with sarcoma or mesothelioma found no definite cardiotoxicity in 18 patients who received more than 500 mg/m^2, 10 of whom received >700 mg/m^2 [18, 19]. A retrospective study in gynecological cancer found only 3 of 53 patients at high risk of doxorubicin-induced cardiotoxicity developed HF possibly related to PLD [24].

Because doxorubicin is a highly effective anti-neoplastic agent, and doxorubicin-induced HF is a serious toxicity, a number of approaches have been used to predict the development of doxorubicin-induced HF. The most widely used approach has been serial monitoring of EF by multigated acquisition (MUGA) or echocardiogram (ECHO) and limiting the total doxorubicin dose. Biomarkers such as troponin, N-terminal brain natriuretic peptide, and brain natriuretic peptide, or clinical assessment for signs and symptoms of heart failure are also used to assess cardiotoxicity.

Ejection fraction has been shown to be a useful measure of cardiac function in some settings, especially HF. However, HF is a clinical syndrome, while EF is a measure of left ventricular function that is very load dependent; they are not one and the same. For example, a modestly low EF may or may not be associated with HF. A reduction in EF should be viewed as a "biomarker" that is associated with HF or may predict the development of HF. It is, of course, widely used to monitor doxorubicin toxicity in patients receiving doxorubicin, and doxorubicin use is often limited on the basis of EF measurements; however, the use of EF is not without its shortcomings. Despite a number of guidelines for monitoring cardiotoxicity with doxorubicin [25], the evidence for the utility of such recommendations is limited. Monitoring EF adds significant costs [24], and MUGA is associated with radiation exposure as well. In addition, if the results are misleading, a patient may be denied further treatment with a drug for treating their cancer.

In this study a retrospective review of 56 patients followed long-term in one practice who received high doses of PLD, sometimes after previous free doxorubicin exposure, was performed to examine the incidence of doxorubicin-induced HF. Our experience in this study made us aware of the serious limitations of EF monitoring to measure the sequential cardiotoxicity of PLD, and other drugs as well, and has the potential risk of inappropriately altering treatment.

Methods

A retrospective chart review was conducted of patients who received a large cumulative dose of PLD between 1997 and 2017, and were seen by one clinician. In addition, published data from three phase II trials of PLD performed at our institution [18, 19, 26] were also reviewed. Two additional patients who had abnormal EF at diagnosis were also included for illustration. This study was approved by the University of Minnesota Institutional Review Board. As most patients were not on a study, the timing of cardiac function tests was not standardized, as it was part of routine clinical care. Some patients received free doxorubicin, as indicated, before receiving PLD. Most determinations of EF were obtained by MUGA, although in some cases echocardiography (ECHO) was used, as indicated in the Supplementary Table.

Results

Fifty-six patients who received >450 mg/m^2 of doxorubicin (free doxorubicin combined with PLD) were reviewed. Of these, 49 received >500 mg/m^2, 28 > 700 mg/m^2, 19 > 800 mg/m^2, 14 > 1000 mg/m^2, and 5 > 1400 mg/m^2 (Tables 1; Supplementary Table). There were 32 men and 24 women with a median age at the first doxorubicin dose of 54 (range 15–93). Two other patients (#57 and 58) had an abnormal baseline EF in the absence of symptoms that later normalized. Forty-five patients were followed for >1 year from the start of doxorubicin treatment (range 10–336 months, median 54 months). No follow-up time was available for 10 patients previously reported in earlier studies [18, 19, 26]. In addition, two other patients with existing doxorubicin-induced HF were treated with PLD without clinical deterioration of HF (not shown). The distribution of PLD vs CIVI free doxorubicin vs bolus free doxorubicin is shown in Fig. 1 and Supplementary Table.

Two findings are noteworthy. Clinical HF clearly related to doxorubicin was not observed, yet seemingly random changes in sequential measurements of EF were frequently noted, not surprisingly (Fig. 2; Supplementary Table). Within the "normal range" of EF (50–78% for men and 50–87% for women), the measurement varied greatly over time in patients in the absence of symptoms or signs of heart disease (Fig. 2). This is not unexpected and well known to cardiologists, as loading conditions and heart rate can change minute-to-minute, and change left ventricular performance independent of any change in intrinsic contractility. In 17 patients the EF changed by ≥10%, or became abnormal. The EF decreased by >10% within the normal range in 6 patients, and the EF increased by >10% (in 1 by >20%) within the normal range in five patients. The EF became abnormal in five patients, all of whom had a later EF that was in the normal range (patients 10, 15, 16, 32, 34); in one it later became abnormal again (#16). In three other patients the EF was abnormal at the start but rapidly normalized in two (Supplementary Table, patients #57 and 58) and remained abnormal without symptoms in 1 (#24). No patient discontinued PLD due to a change in EF. Most of the EFs in the current study were determined by MUGA (Supplementary Table). It should be noted that a reduction in EF related to chemotherapy may later improve, and then become reduced remote from the time of chemotherapy.

ACE inhibitors and beta-blockers may have a protective effect against the development of HF [27, 28], although this has not been shown in a randomized trial. We therefore determined whether patients were seen by a cardiologist or treated with these agents (Table 1). Six patients were treated at some point with one of these agents, 31 were not, and data were not available for 18 cases.

Discussion

In this study a retrospective review of patients who received ≥450 mg/m^2 doxorubicin as PLD and/or free doxorubicin treated in one practice was performed to examine the incidence of doxorubicin-induced HF. In the current study no clear doxorubicin-induced HF was seen in 56 patients who received >450 mg/m^2 total doxorubicin dose. Of these, 49 received >500 mg/m^2, 28 > 700 mg/m^2, 19 > 800 mg/m^2, and 14 > 1000 mg/m^2. Two patients with pre-existing doxorubicin-induced HF were also treated with PLD without adverse effects (not shown here). An additional observation was the prominent variability in the measured EF within patients in the absence of any clinical signs or symptoms of heart disease. These random changes in EF over time are not unexpected, and may be related to changing cardiac loading conditions (Table 2).

These findings are in marked contrast to earlier reports using bolus administration of free doxorubicin. When given by bolus administration the incidence of doxorubicin-induced HF is dose-related, and has been reported to increase from ~7% at 550 mg/m^2 to ~35% at 700 mg/m^2 to ~50% at 1000 mg/m^2 [2, 29]. When combined with previous reports [18, 19, 21–24, 29] of patients receiving high doses of PLD, >140 patients have been treated with >500 mg/m^2 PLD or PLD combined with free doxorubicin without the development of PLD-related HF.

Many of the cases described here are notable for the long follow-up after doxorubicin exposure. However, much longer-term effects would not be detected with the current study even though some patients were followed for >10 years. In one large study ~98% of cases of "cardiotoxicity" identified by EF occurred within 1 year of completion of chemotherapy [28]. The range of time between the last dose of doxorubicin and the onset of doxorubicin-induced HF is broad, ranging from days to years [1, 15, 30, 31]. Some pediatric and adult cancer survivors have been found to develop cardiomyopathy years after treatment with doxorubicin [30–35]. Some animal models also demonstrate progressive doxorubicin-induced cardiomyopathy, and a similar effect is seen with PLD [15]. In addition, genetic variants appear to correlate with the development of doxorubicin-induced cardiotoxicity in children [31]. The findings of the current study may not apply to children.

Several approaches have been taken to try to reduce anthracycline cardiotoxicity, including the use of angiotensin converting enzyme inhibitors and beta-blockers [27, 28], a heavy metal chelator [36], and anti-inflammatory drugs [37]. The use of dexrazoxane from the start of bolus doxorubicin may reduce long-term cardiotoxicity; none of the patients in this study received dexrazoxane. The peak serum level of doxorubicin is important in the induction of cardiotoxicity, and the administration of doxorubicin by CIVI over longer

Table 1 Patient characteristics

Patient	Age (years)	Sex	Diagnosis	Other chemotherapy	Comorbidities	Method of free doxorubicin administration	Cumulative doxorubicin dose (free and PLD) received (mg/m^2)	Last follow-up (months)	ACE inhibitors or beta-blockers added	Seen by Cardiology
1	76	Male	UPS	Gemcitabine, ifosfamide, etoposide	Chest radiation therapy, radiation pericarditis, rectal cancer, CVA, left bundle branch block		545	142	No	Yes
2	61	Male	Liposarcoma	Spine radiation therapy, CKD, hemodialysis			1387	54	No	No
3	58	Male	Mesothelioma				2001	52	No	No
4	68	Female	Mesothelioma				1544	53	NA	NA
5	44	Male	Synovial sarcoma	Gemcitabine, sunitinib		Civi	801	84	NA	NA
6	50	Male	Angiosarcoma, received Taxol first	Paclitaxel			1775	100	No	Yes
7	64	Female	Angiosarcoma				630	115	No	No
8	57	Male	UPS				495	52	No	No
9	80	Female	Kaposi		Diabetes, depression		1060	99	Yes	Yes
10	22	Female	Aggressive fibromatosis	Methotrexate, vinblastine, ifosfamide, etoposide, gemcitabine, sunitinib	Depression, GERD		464	176	No	No
11	65	Female	LMS	Ifosfamide			790	23	NA	NA
12	47	Male	Extraskeletal myxoid chondrosarcoma	Ifosfamide, etoposide, sunitinib, gemcitabine			503	35	No	No
13	64	Male	Hodgkin disease	Bleomycin, vincristine, DTIC, ifosfamide, etoposide, cyclophosphamide, gemcitabine, navelbine, BMT	H/O heart disease, CAB age 54, MI, stent, BMT	Bolus	1555	59	Yes	Yes
14	59	Male	Kaposi sarcoma		Liver transplant, hepatitis C, diabetes		1480	112	NA	NA
15	49	Female	Breast Ca AC/Taxol, then Xrt induced sarcoma at age 57	Cyclophosphamide, paclitaxel, chest wall radiation therapy		Bolus then Civi	540	193	No	No

Table 1 (continued)

Patient	Age (years)	Sex	Diagnosis	Other chemotherapy	Comorbidities	Method of free doxorubicin administration	Cumulative doxorubicin dose (free and PLD) received (mg/m^2)	Last follow-up (months)	ACE inhibitors or beta-blockers added	Seen by Cardiology
16	85	Male	Kaposi sarcoma		Baseline CAD At time minus 16 months, pemphigus, depression, MI, stent multiple medical problems		1182	63	Yes	Yes
17	30	Male	Desmoid	Ifosfamide	Familial polyposis, depression, abdominal fistula		1328	74	No	No
18	–	Female	LMS	Na	Na	Civi	517	NA	NA	NA
19	–	Male	Ewing	Na	Na	Civi	>1050	NA	NA	NA
20	–	Male	UPS	Na	Na	Civi	641	NA	NA	NA
21	–	Male	Osteosarcoma	Na	Na	Civi	714	NA	NA	NA
22	–	Male	GIST	Na	Na	Civi	790	NA	NA	NA
23	–	Male	UPS	Na	Na	Civi	671	NA	NA	NA
24	–	Female	Osteosarcoma	Na	Na	Civi	658	NA	NA	NA
25	–	Female	Osteosarcoma	Na	Na	Civi	752	NA	NA	NA
26	–	Female	Ewing	Na	Na	Civi	1334	NA	NA	NA
27	–	Male	UPS	Na	Na	Civi	1221	NA	NA	NA
28	55	Female	UPS, had hodgkin treated at age 29 W XRT then Bleo-CCVPP a year later	Bleo-CCVPP, chest and abdominal radiation therapy, ifosfamide, etoposide, DTIC, gemcitabine, pazopanib	Diabetes		783	93	No	No
29	73	Male	Angiosarcoma	Paclitaxel			673	27	NA	No
30	60	Female	Sarcoma, NOS	Ifosfamide, gemcitabine		Civi	805	18	No	No
31	22	Female	Ewing	Cyclophosphamide, ifosfamide, etoposide		Civi	703	34	No	No
32	24	Male	Osteosarcoma	Cisplatinum, methotrexate, chest radiation therapy	Tracheal esophageal fistula, radiation pericarditis with tamponade	Civi	465	50	Yes	Yes
33	50	Male	Fibrosarcoma				576	39	NA	NA

Table 1 (continued)

Patient	Age (years)	Sex	Diagnosis	Other chemotherapy	Comorbidities	Method of free doxorubicin administration	Cumulative doxorubicin dose (free and PLD) received (mg/m^2)	Last follow-up (months)	ACE inhibitors or beta-blockers added	Seen by Cardiology
34	58	Male	Kaposi sarcoma	Paclitaxel	AIDS, HIV anti-retroviral therapy, COPD, depression, iv drug abuse		>780	159	Yes	Yes
35	46	Male	Synovial	Ifosfamide, DTIC mitomycin C, cisplatinum, pazopanib, eribulin, trabectedin			572	24	No	No
36	69	Male	Epithelioid sarcoma		CAD, diabetes, HBP, chronic kidney disease (CKD), malignant pleural effusion		873	28	Yes	Yes
37	45	Female	Radiation-induced sarcoma	Paclitaxel, cyclophosphamide, ifosfamide	Breast cancer W ACx6, Taxol, tamoxifen, aromatase inhibitor	Bolus	1170	174	No	No
38	34	Male	Ewing	Cyclophosphamide, vincristine, ifosfamide, etoposide, sunitinib, gemcitabine		Civi	710	30	NA	NA
39	79	Female	High-grade fibrosarcoma		Vasculitis		633	56	No	No
40	54	Male	Myxoid liposarcoma	Gemcitabine, trabectedin			547	31	No	No
41	70	Female	Radiation-induced UPS	Gemzar, radiation, immune colitis	PE, ureteral obstruction, bone pain		630	31	No	No
42	57	Male	UPS	Ifosfamide, gemcitabine, sunitinib			495	48	No	No
43	48	Female	Cutaneous T-cell lymphoma, (large cell, CD30-positive transformation)	Targretin, chlorambucil, cyclophosphamide, vincristine, brentuximab		Bolus	1232	85	NA	NA
44	67	Male	Angiosarcoma	ifosfamide			540	26	No	No
45	59	Female	Angiosarcoma	ifosfamide			489	26	No	No
46	51	Female	Extraskeletal myxoid chondrosarcoma	Radiation therapy			950	25	No	No

Table 1 (continued)

Patient	Age (years)	Sex	Diagnosis	Other chemotherapy	Comorbidities	Method of free doxorubicin administration	Cumulative doxorubicin dose (free and PLD) received (mg/m^2)	Last follow-up (months)	ACE inhibitors or beta-blockers added	Seen by Cardiology
47	41	Female	UPS	Ifosfamide			601	23	No	No
48	93	Male	Kaposi sarcoma	Radiation therapy	DM, CVA, neuropathy, osteomyelitis, macrocytic anemia		724	33	No	Yes
49	63	Male	Dedifferentiated liposarcoma	Ifosfamide			691	23	No	No
50	82	Female	Dedifferentiated liposarcoma		History of takutsubo cardiomyopathy, GERD		625	14	No	Yes
51	32	Female	NHL with CHOP and radiation therapy at age 32, then radiation-induced UPS age 43	Doxorubicin Cyclophosphamide Vincristine Prednisone Leg radiation ifosfamide	NHL, DVT, GERD, history of AKI	Bolus	959	266	No	No
52	57	Female	UPS	Ifosfamide			484	17	No	No
53	33	Male	Kaposi sarcoma	Doxorubicin (treated elsewhere)	DM, tuberculosis	Bolus	>619	105	No	No
54	15	Male	Osteosarcoma	ifosfamide, methotrexate, carboplatin, etoposide,	CKD, thoracotomy x5	Civi	640	336	No	No
55	64	Female	Ewing sarcoma	Cyclophosphamide, vincristine, ifosfamide, etoposide, XRT	HBP, B12 deficiency, splenectomy, hyperlipidemia	Civi	690	149	No	No
56	39	Male	Synovial sarcoma	Ifosfamide, denosumab,	Bone pain, nephrolithiasis		490	10	No	No
57	23	Female	Non-Hodgkin lymphoma	Cyclophosphamide, vincristine, rituximab		Bolus	300	24	No	Yes
58	63	Female	Myxoid liposarcoma				348	12	No	Yes

Age age at first doxorubicin, *UPS* undifferentiated pleomorphic sarcoma, *civi* continuous intravenous infusion, *CVA* cerebrovascular accident, *CKD* chronic kidney disease, *NA* not available, *GERD* gastroesophageal reflux disease, *LMS* leiomyosarcoma, *CAD* coronary artery disease, *CAB* coronary artery bypass, *MI* myocardial infarction, *BMT* bone marrow transplant, *AC* doxorubicin and cyclophosphamide, *XRT* radiation therapy, *GIST* gastrointestinal stromal tumor, *Bleo-CCVPP* bleomycin, cyclophosphamide, lomustine, vincristine, procarbazine, and prednisone, *DTIC* dacarbazine, *HBP* hypertension, *NOS* not otherwise specified, *COPD* chronic obstructive pulmonary disease, *DM* diabetes, *CRF-D* chronic renal failure on dialysis, *PE* pulmonary embolus, *AIDS* acquired immune deficiency disease, *CHOP* cyclophosphamide, doxorubicin, vincristine, prednisone, *DVT* deep venous thrombosis, *AKI* acute kidney injury

Data from subjects 18–27 are from previously published studies and the age was not published

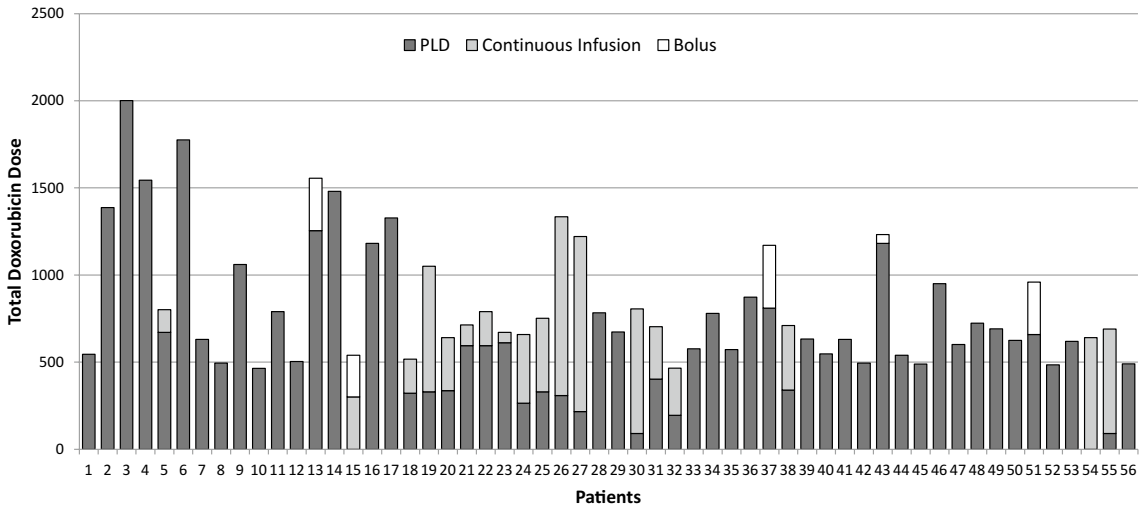

Fig. 1 Histogram of doxorubicin dose by formulation and type of administration (PLD, solid; civi, shaded; bolus, open). For patient #19 the minimum amount of free doxorubicin is shown (exact amount unknown). For patient #34 the minimum amount of PLD is shown (exact amount of unknown). For patient #53 the minimum amount of PLD is shown (exact amount of unknown)

times has been shown to reduce cardiotoxicity in adults [1, 4–10]. PLD leaves the vascular space at a much slower rate than free doxorubicin, and many studies have reported less cardiotoxicity with PLD than with free doxorubicin [14–24, 29]. Reduced risk of cardiotoxicity is not equal with all liposomal formulations [38]; thus, the conclusions of studies using PLD may not apply to other liposomal doxorubicin formulations that have different stability properties.

Despite the wide use of EF to monitor doxorubicin cardiotoxicity, and the existence of a variety of guidelines and recommendations, the utility of serial EF measurements to predict doxorubicin-induced HF is unclear. This is in part due to the fact that a low EF and heart failure are not the same. One is a measurement, and the other is a clinical syndrome; they don't have to co-exist. Patients may also have HF with a preserved EF. EF may change modestly from day-to-day in normal subjects, depending on hydration status, similar to blood pressure and heart rate; this is also true in patients being treated with doxorubicin. In addition to the normal day-to-day variation in EF, there is inter- and intra-observer variation in the reading of EF by ECHO. This is especially true when the EF is simply "estimated" by the echocardiographer without objective measurements. It is generally preferred that the ECHO EF be calculated, not estimated, as this tends to lower the degree of intra- and inter-observer variation. When MUGA is used, the EF is always calculated mathematically, so the measurement is considered more precise. Most of the EFs in the current study were determined by MUGA (Supplementary Table).

In addition to physiologic variation, the measurement of EF may not be accurate. Although EF determined by 3-dimensional echocardiography can vary by ~0.05–0.06 (absolute change in EF) due to physiologic changes or test reproducibility [39], with 2-dimensional echocardiography this variability can be ~0.10–0.13 [39], with ~11% being the smallest change in EF that can be recognized with 95% confidence [40]. Although MUGA scans are more accurate, there is still variability in the EF measured by this technique. In one study the 95% CI was −5.4 to +6.4 for inter-observer variability and −4 to +3.5 for intra-observer variability [41]. In a related study, the inter-study variability on patients who were scanned twice on CZT-SPECT cameras had 95% CI of −5.4 to +6.4 [42]. Thus, the limitations of EF measurement must be considered in the interpretation of EF changes. As shown in this series of 53 cases, the EF can vary prominently over time in the absence of cardiac symptoms. It is noteworthy that the early angiographic determination of the EF in normal subjects was limited to <10 subjects.

In the absence of clinical symptoms, the definition of cardiotoxicity is not exact. Some definitions of cardiotoxicity have utilized a decrease in EF of ≥5 to <55% with symptoms of HF, or a decrease in EF of ≥10 to <55% in asymptomatic patients, though other definitions are also used [39, 43, 44]. However, as discussed above, EF varies somewhat even throughout the day in normal people, and in the absence of clinical symptoms, the utility of EF changes to predict doxorubicin-induced HF is unproven.

An analysis of three phase 3 studies found that the left ventricular EF was not an accurate predictor of the development of doxorubicin-induced HF [2]. A study of 20 patients with EF <50% undergoing bone marrow transplant found no difference in survival as compared with 288 patients with

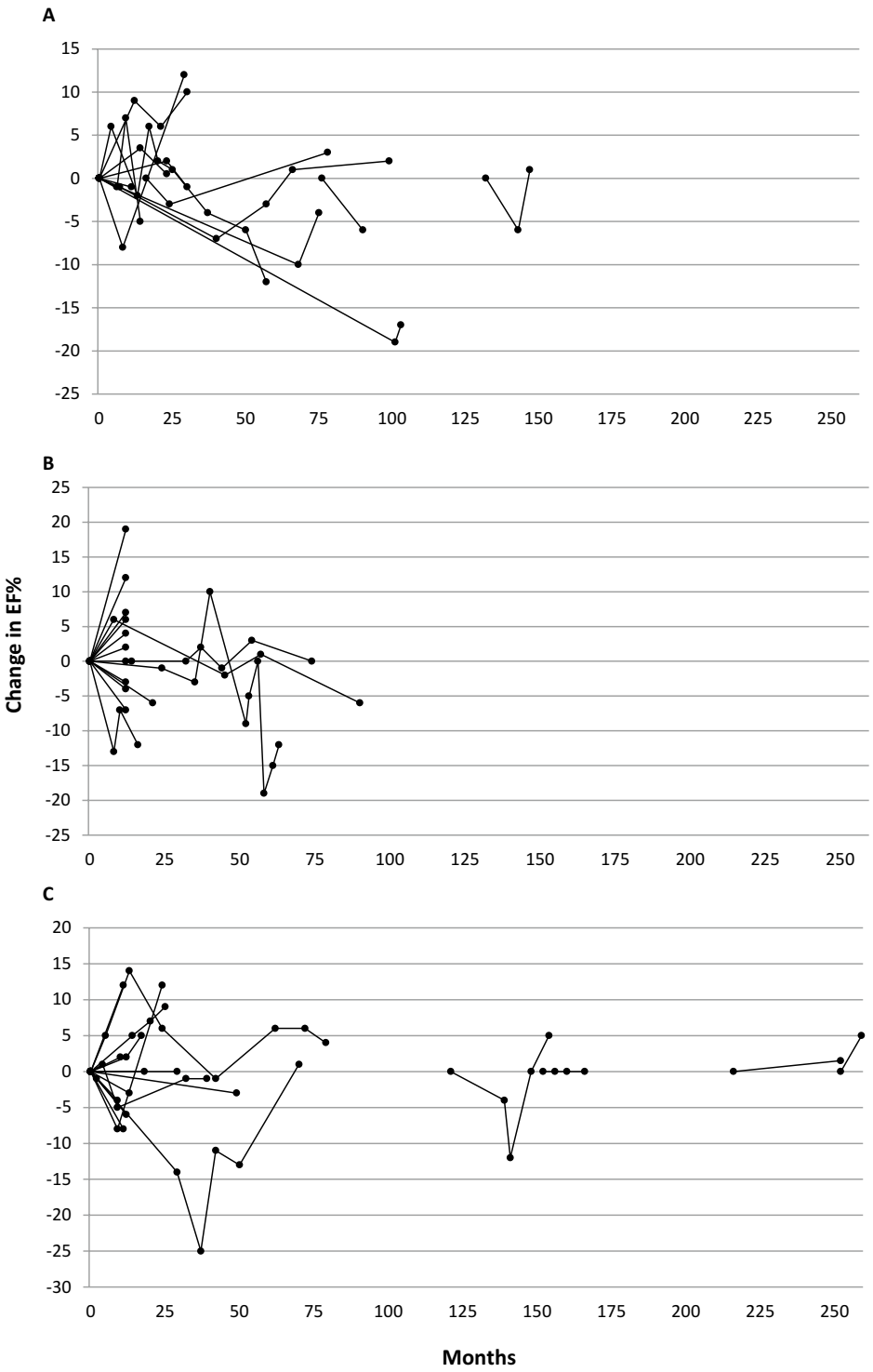

Fig. 2 Ejection fraction variability of 58 patients who received large cumulative doses of doxorubicin as pegylated-liposomal doxorubicin. **a** Patients 1–15. **b** Patients 16–30. For patients 18–27, the final EF is shown at 12 months, although the time of the final EF is unknown. **c** Patients 31–58

preserved EF [45]. A similar finding was seen in a study of 49 patients with EF <50% as compared with 49 controls [46]. The lack of clear benefit of EF monitoring could be due to several factors: intrinsic variability of measuring EF at a given time, random variability of EF over time in normal and abnormal hearts within patients, variation in intravascular volume status when EF is measured, and when the EF is determined in relation to the last dose of the cardiotoxic agent. Further confounding factors include: when and to what degree cardiotoxicity will develop in relation to when and to what degree EF changes occur, and when will cardiotoxicity develop following exposure to a cardiotoxic agent.

Table 2 Cumulative dose of PLD + free doxorubicin

Total doxorubicin dose (mg/m2)	Number of patients
450–499	7
500–599	8
600–699	13
700–799	9
800–899	3
900–999	2
1000–1099	2
1100–1199	2
1200–1299	2
1300–1399	3
1400–1499	1
1500–1599	2
1600–1699	0
1700–1799	1
>2000	1

Finally, if some degree of cardiotoxicity is noted at one time point after cardiotoxin exposure, what is the natural history of cardiac function in the absence and presence of additional cardiotoxin exposure? That is, will changing treatment alter further change in EF, and to what degree does a change in EF alter clinical outcome.

This study is subject to the usual limits of a retrospective study. In addition, as described above, the diagnosis of HF is subjective, and the physicians treating the patients in this study might differ from others in their use of the term. However, the doses received and long-term follow-up are noteworthy. In addition, the observed changes in EF within patients over time, and the range of time over which doxorubicin-induced cardiotoxicity can be observed (days to years), along with the variable time between drug exposure and EF determination, suggest that the routine use of measurements of left ventricular EF to direct doxorubicin use is open to question and needs further study before it can be accepted as a useful approach. An attractive study would be a randomized trial to examine whether monitoring EF can truly predict later significant doxorubicin cardiotoxicity, and whether the medical treatment of asymptomatic EF changes impacts later functional outcome.

This report provides further evidence for the low risk of cardiotoxicity with PLD and CIVI doxorubicin. In addition, the "normal" fluctuations in EFs observed over time, and the potential for cardiotoxicity developing long after doxorubicin exposure, raise the question of the utility of routine cardiac monitoring during doxorubicin administration. While cardiologists are familiar with the limitations of the use of EF, many oncologists may not be. In addition such monitoring adds to the cost of health care. The Medicare fee rates for an ECHO or MUGA scan are in the range of ~$365–890 and $840–2300, respectively [24]. Given the reduction in doxorubicin-induced HF when doxorubicin is given by CIVI or as PLD, and the limited predictive value of EF in predicting doxorubicin cardiotoxicity, the monitoring of EF during treatment is not of proven value. Indeed, as has been suggested, given the prognosis of many patients receiving these drugs, erroneous interpretation of EF changes might inappropriately limit their access to a useful drug [21, 24]. This question is also relevant to the use of EF to monitor cardiotoxicity in other cancer drugs [35, 47], which are also widely used, where the increased cost and true utility are also important. A number of other approaches to predicting doxorubicin-induced cardiomyopathy are under study, although the relationship of early test results with long-term effects will require detailed follow-up [48, 49]. For example, in a small study, the sensitivity to doxorubicin of cardiomyocytes derived from induced stem cells from dermal fibroblasts correlated with the development of doxorubicin-induced HF in the donor [50].

In conclusion, our results question the utility of sequential measurement of EF to guide doxorubicin dosing in the case of adults treated with PLD and also in the setting of doxorubicin given by CIVI. In addition to the expense of testing and the lack of clear benefit in reducing doxorubicin-induced HF, random variation in EF measurement may lead to depriving some patients of a useful treatment. These results may not apply to all liposomal formulations or to children. We agree with Gill et al. and Kushnir et al. [21, 24] that the routine surveillance of EF, at least in adults with PLD in the absence of serious risk factors, does not seem warranted. Even with serious risk factors the utility of cardiac monitoring is seemingly limited.

Compliance and ethical standards

Funding This study received no funding.

Conflict of interest Dr. Skubitz has received research funding from Johnson & Johnson or its subsidiaries and has owned publicly traded stock in JNJ in the past. The other authors have no potential conflict.

Ethical standards This study was approved by the University of Minnesota IRB and was performed in accordance with the ethical standards of the institutional IRB and the 1964 Helsinki declaration and its later amendments.

Human and animal rights This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was not obtained, per the approval of the University of Minnesota IRB, as it was a retrospective study, no identifying information is presented, and many of the patients are no longer living.

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