Anthracycline-induced cardiotoxicity and the cardiac-sparing effect of liposomal formulation

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Abstract: The anthracyclines are a group of antibiotics that are among the most potent chemotherapeutic agents. They are highly effective against a broad spectrum of malignancies, including lymphoma, gastric cancer, small cell lung cancer, sarcoma, and breast cancer. Unfortunately, these agents also exhibit a well-recognized cumulative-dose related cardiotoxic profile that limits the extent to which they can be used safely. In clinical practice, most clinicians limit the cumulative dose of doxorubicin (the most widely used agent in this group) to 400–450 mg/m^2, but considerable cardiac damage is now known to occur at cumulative dosages considerably below this level. Regimens using newer combinations of agents, the most widely studied of which is the monoclonal antibody trastuzumab, are known to augment the cardiotoxicity of anthracyclines. The application of nanotechnology to medicine involves the use of devices that will interact with the body at the molecular level. These methods can lead to target and tissue specific clinical application, often with minimal or reduced side effects. Liposomal preparations incorporate such technology, thereby altering some important characteristics of the parent compound and facilitating concentration at the tumor site. In the case of liposomal doxorubicin, cardiotoxicity is reduced significantly. This review summarizes the important information on the liposomal preparation of anthracyclines.

Keywords: anthracycline, cardiotoxicity, liposomal, cardioprotection

Introduction

The anthracyclines are a group of antibiotics that are among the most active chemotherapeutic agents. They are highly effective against a spectrum of malignancies including both hematological and solid tumors including lymphoma, gastric cancer, small cell lung cancer, sarcoma, and breast cancer (Table 1). Some of the commonly used anthracycline antibiotics include doxorubicin, daunorubicin, and epirubicin. Unfortunately, these agents also exhibit a well-recognized cardiotoxic profile that places limits on the extent to which these lifesaving agents can safely be used. In clinical practice, most clinicians limit the cumulative dose of doxorubicin, the most widely used agent in this group, to 400–450 mg/m^2. Thus, limiting total cumulative dose creates a dilemma of having to balance suboptimal oncologic treatment with a proven beneficial therapy against that of the risk of cardiotoxicity. Regimens of combination chemotherapy that includes newer agents such as taxanes and trastuzumab are clearly effective but have resulted in problematic cardiotoxicity. As such, numerous techniques have been employed in an attempt to mitigate the cardiotoxicity of the initial anthracycline exposure, thereby preserving the myocardial reserves.

Moreover, as the number of long-term survivors including pediatric cancer patients increases, more elderly patients with pre-existing cardiovascular co-morbidities are given chemo-radiation therapies, and as use of combination immuno-chemotherapy with overlapping toxicities (eg, trastuzumab, taxanes, and anthracyclines) increase, cardiotoxicity is increasingly becoming a very important issue today in cancer therapy.

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Table 1 Malignancies commonly treated with anthracyclines

Malignant lymphoma
Soft tissue and bone sarcoma
Acute lymphoblastic leukemia
Ovarian carcinoma
Breast cancer
Neuroblastoma
Transitional cell bladder carcinoma
Thyroid carcinoma
Gastric carcinoma
Wilm's tumor
Bronchogenic carcinoma (small cell)
AIDS-related Kaposi's sarcoma

Nanotechnology can be defined as the science and engineering involved in the design, synthesis, characterization, and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometer scale or one billionth of a meter. It is a scientific field devoted to the manipulation of atoms and molecules to construct miniature structures for new molecular assemblies at the nanometer scale size.

The application nanotechnology to medicine involves use of devices that will interact with the body at the molecular level. These methods will have high degrees of specificity and can lead to target and tissue specific clinical applications with minimal side effects.

Some examples of such applications of nanotechnology to medicine includes development of novel drug delivery systems, chemically functionalized dendrimers that can be used as molecular building blocks for gene therapy agents or as magnetic resonance imaging (MRI) contrast agents (Silva 2004).

One of the most important clinical applications of nanotechnology appears to be in pharmaceutical development. Some of the emerging applications involve new approaches for controlled release of the drug, drug targeting, and targeting the organ to minimize side effects. One such example is the use of nanoscale polymer capsules that are designed to break down and release drugs at controlled rates and to allow differential release in certain environments, such as an acid milieu, to promote uptake in tumors versus normal tissues (Na and Bae 2002).

The use of nanotechnology is useful to increase the tissue availability of drugs with low bioavailability. Hydrophobic drugs such as paclitaxel or 5-fluorouracil can be encapsulated in polymers or liposomes with nanoscale cavities that improve drug absorption and bioavailability.

Nanoparticles in cancer may be used for various functions including tumor tissue and cells targeting and delivery, and for qualitative or quantitative in vitro detection of tumor cells (Brigger et al 2002).

The use of nano- and microparticle-based imaging of cardiovascular interventions is still in its developing phase, but in future may be used as a diagnostic imaging agent, function as a therapeutic carrier, be used as particle-mediated imaging of primary gene and drug delivery, and be used for follow-up gene therapy (Yang 2007). Hence it is not only applicable for diagnostic, therapeutic purposes but also to monitor therapeutic efficiency after interventions performed to treat cardiovascular diseases.

This review summarizes important information about the effects of anthracyclines and the available data on liposomal formulations, one of the most important strategies of cardioprotection, and expands and updates previous reviews (Ewer 2004).

Definition of cardiotoxicity

Antracycline-induced cardiotoxicity was first described in the 1970s. At that time anthracycline-associated cardiotoxicity was thought of as a cumulative dose-related form of congestive heart failure (CHF) that was rapidly progressive if use of the agent was continued. Von Hoff et al (1979) provided important initial insight regarding clinically manifested CHF. Increased awareness of sub-clinical cardiac impairment resulting from these agents has led to improved screening as well as a better perspective of the inherent toxicity of these agents. Today's definition has expanded from the clinical events of cardiac failure to include a wide spectrum of predefined laboratory values even when patients may be asymptomatic. These include histological changes (Billingham and Bristow 1984) in the cardiomyocytes (Table 2), and changes in left ventricular ejection fraction (LVEF) based on either radionuclide ventriculography (Schwartz et al 1987) (RNVG) or two-dimensional (2D)-echocardiography (Stoddard et al 1992). Even transient changes previously thought to be not of any major clinical significance, eg, daunorubicin-induced myocarditis/pericarditis (Topalov et al 1981; Gaudin et al 1993) will now be considered as anthracycline-induced cardiomyopathy. The general consensus is that a decrease in LVEF by more than 20 percentage points to a value $>50\%$, a decrease in LVEF by more than 10 percentage points to a value $<50\%$, or clinical manifestations with signs and symptoms of CHF constitute cardiotoxicity. Others have combined these criteria to define cardiotoxicity as a decrease in LVEF by more than 10 points to a final value of $<50\%$ (Ganz et al 1993).

Incidence of cardiotoxicity with conventional anthracyclines

Using the refined criteria, in large clinical trials, approximately one in four patients experienced congestive heart

Table 2 Morphologic grading systems for anthracycline cardiotoxicity

Grade	Billingham scoring system (Billingham et al 1978) morphologic characterics	Mackay scoring system (Mackay et al 1994; Ewer et al 1984)		
		Vacuoles	Myofibrillar dropout	Necrosis
0	Normal myocardial ultrastructural morphology			
0.5	Not completely normal but no evidence of anthracycline-specific damage	<4	0	1
1	Isolated myocytes affected and/or early myocfibriller loss; damage to <5% of all cells	4–10	<3	1
1.5	Changes similar to grade 1 except damage involves 6%–15% of all cells	>10	3–5	<2
2	Clusters of mycocytes affected by myofibrillar loss and/or vacuolization, with damage to 16%–25% of all cells	any number	6–8	2–5
2.5	Many mycocytes (26%–35% of all cells) affected by vacuolization and/or myofibrillar loss	(The grade of 2.5 is not included in the Mackay grading system)		
3	Severe, diffuse myocyte damage (>35% of all cells)	any number	>8	>5

failure when the cumulative dose of doxorubicin exceeded 500 mg/m^2, nearly 50% had cardiac events above 600 mg/m^2, and nearly all patients had cardiotoxicity above 800 mg/m^2. The incidence of clinical cardiac failure increases precipitously above 550 mg/m^2 (Von Hoff et al 1979) with the majority developing cardiomyopathy within the first year of completion of treatment. More recent data, however, suggest that cardiomyopathy not only develops at a much lower cumulative dose than previously thought, but it may also manifest even years after treatment, especially in pediatric oncology survivors (Lipshultz et al 1991; Steinherz et al 1991; Hequet et al 2004). An analysis by Steinherz et al (1991) of 201 long-term childhood cancer survivors 4–20 years after completion of anthracycline-based chemotherapy showed almost a quarter of the patients remain at risk for developing cardiomyopathy even years after exposure. Cardiac biopsy as well as newer imaging techniques suggest that cardiac damage almost certainly takes place from the onset of anthracycline exposure irrespective of its detection by conventional non-invasive cardiac parameters.

Risk factors for anthracycline-induced cardiotoxicity

Complete details regarding the risk factors are beyond the scope of this review. In brief, the recognized risks besides the cumulative anthracycline dose include age (elderly and young), mediastinal irradiation or radiotherapy to the left chest, other cardiac risk factors such as hypertension, female gender (especially in the pediatric population), previous exposure to any anthracycline, coadministration of other anticancer drugs, and methods of administration (bolus vs protracted infusion) (Von Hoff et al 1979; Steinherz et al 1991; Anon 2000; Hequet et al 2004). Other natural phenomena in these immunocompromised populations such as infections that involve the myocardium may constitute sequential stresses that when superimposed on an impaired myocardium may result in life-threatening or disabling heart failure (Ali et al 1994). Given that the two leading causes of death in the United States are cardiovascular diseases and malignant neoplasms (Anon 2006; Banks et al 2006), in an increasingly aging population, patients with cancer are ever more likely to have other co-morbidities, in particular diseases of the cardiovascular system, making them more susceptible to chemotherapy-induced cardiomyopathy. Additionally, cardiac risk factors such as hypertension, hyperlipidemia, and diabetes (Zambetti et al 2001), although unrelated to anthracycline toxicity, may also contribute to the progression of cardiac damage and clinical cardiotoxicity.

Pathology of anthracycline-induced cardiotoxicity

Early morphologic changes include cytoplasmic vacuolization and myofibrillar loss of myocytes caused by dilatation of the sarcoplasmic reticulum (Figure 1, Table 2). In more advanced cases, such cellular changes lead to cardiac remodeling and eventually to left ventricular failure with increased mortality (Billingham et al 1978; Von Hoff et al 1979). The mechanism of conventional doxorubicin-induced myocardial damage is not exactly known but is believed to involve production of free radicals that induce peroxidation of myocyte membranes and subsequent influx of intracellular calcium (Andrieu-Abadie et al 1999; Falcone et al 1998). One source of such reactive oxygen intermediates is the formation of conventional doxorubicin-iron complexes in mitochondrial membranes that may

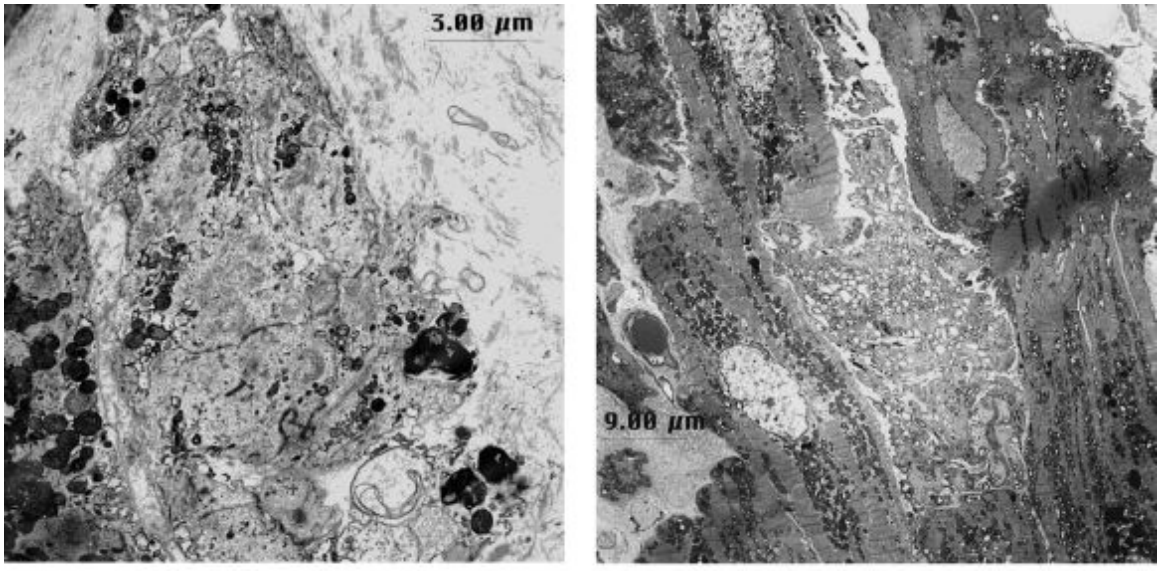

Figure 1 Electron micrographs showing examples of representative field of a high-grade biopsy (Billingham score of 3.0) obtained from a solid-tumor patient who received more than 400 mg/m^2 conventional doxorubicin. Severe diffuse damage to >35% of all cells was seen. Necrotic cell is shown with extensive myofibrillar loss (**A**). Another cell is seen with extensive vacuolization (**B**, center). Magnification is indicated by a bar in each frame. (Micrographs courtesy of Gerald Berry MD, Stanford University School of Medicine (Ewer et al 2004)).

lead to increased inner membrane permeability in heart mitochondria as a result of increasing the sensitivity of a Ca^{2+} dependent-pore of the inner mitochondrial membrane to calcium, leading to dissipation of membrane potential and release of pre-accumulated Ca^{2+} (Al-Nasser 1998). Mitochondrial dysfunction correlated with morphologic changes seen in cumulative and irreversible cardiotoxicity may also be caused by accumulation and persistence of 8-hydroxyguanosine adducts in cardiac mitochondrial DNA (Serrano et al 1999). Additionally, impaired sequestration of intracellular free calcium ions in individual myocytes as a result of drug exposure may cause impairment of essential fatty acid metabolism (Bordoni et al 1999) and diastolic dysfunction (Maeda et al 1998). Since high cardiac tissue levels of doxorubicinol, a metabolite of the conventional doxorubicin, are associated with both functional and morphologic changes consistent with the anthracycline cardiomyocyte injury, it may be possible to prevent the reductase pathway leading to doxorubicinol production, thereby decreasing cardiotoxicity without impairing the therapeutic efficacy of anthracyclines (Minotti et al 2001). The cytotoxic effect of anthracyclines on cardiomyocytes is generally thought to be irreversible and cumulative dose related. Biopsy data as well as the shape of the dose-response curve provide strong evidence that damage takes place from the time of the initial exposure, despite the fact that cardiac reserves prevent clinical recognition until sufficient damage has taken place to the extent that the compensatory reserve of the heart is exceeded.

Clinical relevance of cardiomyopathy

The reported incidence of anthracycline-associated cardiomyopathy varies widely depending on the way it is ascertained, the setting in which it is studied, and the underlying risk of the patient population. The earliest and the most often cited study was based on a retrospective analysis of patients enrolled in phase II studies of conventional doxorubicin (Von Hoff et al 1979). Cardiomyopathy had not been previously studied and was to some extent the only endpoint recorded in the medical records at the time was clinically manifested heart failure. From a curve relating cumulative dose to the incidence of CHF, it was estimated that after 728 mg/m^2 the probability of developing CHF was in excess of 20%.

However, with advanced imaging techniques and close patient monitoring, the incidence of any form of cardiomyopathy using serial evaluations of left ventricular ejection fraction, may be considerably higher than was reported initially. A pooled analysis of 630 patients who underwent serial evaluations of cardiac function during conventional doxorubicin treatment in three controlled trials reported

a CHF incidence of 26% after a cumulative dose exceeding 500 mg/m^2, 48% for a cumulative dose exceeding 600 mg/m^2, and 100% above 800 mg/m^2 (Swain et al 2003). Subclinical evidence of cardiomyopathy may occur at lower cumulative doses, as suggested by a study of 141 patients who received conventional doxorubicin for lymphoma (Hequet et al 2004); 28% of patients had subclinical cardiomyopathy (defined as left ventricular fractional shortening $<$25%), including 25% of patients who received a cumulative dose 300 mg/m^2. In one study of patients with breast or lung cancer who were treated with a combination regimen that included cyclophosphamide, CHF was observed in more than 20% of those given a cumulative dose of 500 mg/m^2 (Shapiro et al 1998).

Studies where the incidence of CHF was reported to be very low (from 0.2% to 0.9%) used conventional doxorubicin as part of a combination regimen and were used as adjuvant therapy for early breast cancer (Shapiro and Recht 2001). In these studies, the cumulative dose of conventional doxorubicin rarely exceeded 300 mg/m^2 and was usually 240 mg/m^2. However, in subsequent controlled studies in women with breast cancer, the incidence of CHF increased to 4.7% at a cumulative dose of 400 mg/m^2, and 26% at cumulative doses of 550 mg/m^2 (Swain et al 2003). Therefore, while patients may respond favorably to initial anthracycline therapy up to cumulative doses of less than 300 mg/m^2, extra precaution is warranted because of heightened risk of cardiotoxicity before additional conventional anthracycline treatment is started when relapse occurs. Alternative treatments that have comparable or better efficacy but yet have a lower risk of cardiotoxicity may be considered in patients with anthracycline-sensitive tumors.

Cardiotoxicity secondary to treatment with conventional doxorubicin remains a serious problem in survivors of pediatric malignancy long after the cancer has been cured (Lipshultz 2006). In a cohort of 607 children, 2.8% of patients treated with a median anthracycline dose of 301 mg/m^2 developed CHF after a median follow-up period of 6.3 years (Kremer et al 2001). It is estimated that 5% of patients will develop CHF within 15 years after anthracycline treatment. For children receiving a cumulative dose of more than 300 mg/m^2, the relative risk of developing CHF was 11.8-fold greater than for those exposed to less than 300 mg/m^2 (Lipshultz 2006).

Potentiation of cardiotoxicity in combination regimens

Use of trastuzumab either concomitantly or sequentially following anthracycline treatment may potentiate conventional anthracycline-induced cardiotoxicity (Valagussa et al 2001; Genentech 2003), or, more commonly, represents a sequential stress to a previously damaged myocardium. In a pivotal trial to obtain regulatory approval for the use of trastuzumab, patients with metastatic breast cancer who had not previously been treated with adjuvant conventional doxorubicin, a significantly higher incidence of cardiotoxicity was noted in the trastuzumab arm, whether this was measured as "any form of cardiotoxicity" or only grade III/IV cardiotoxicity. Several clinical trials are under way to determine if sequential administration of trastuzumab and conventional doxorubicin is associated with similar chemotherapeutic activity but less cardiotoxicity than concurrent use (Wolff 2003). One such recently published large randomized trial, National Surgical Adjuvant Breast and Bowel Project trial B-31 (Tan-Chiu et al 2005), compared doxorubicin and cyclophosphamide (AC) followed by paclitaxel with AC followed by paclitaxel plus 52 weeks of trastuzumab beginning concurrently with paclitaxel in patients with node-positive, HER2-positive breast cancer. If symptoms suggestive of CHF developed, source documents were blindly reviewed by an independent panel of cardiologists to determine whether criteria were met for a cardiac event, which was defined as New York Heart Association class III or IV CHF or possible/probable cardiac death. Among patients with normal post-AC LVEF who began further treatment, 5 of 814 control patients subsequently had confirmed cardiac events (4 CHFs and 1 cardiac death) compared with 31 of 850 trastuzumab-treated patients (31 CHFs and no cardiac deaths). The difference in cumulative incidence at 3 years was 3.3% (4.1% for trastuzumab-treated patients minus 0.8% for control patients; 95% CI, 1.7%–4.9%). CHFs were more frequent in older patients and patients with borderline post-AC LVEF. Fourteen percent of patients discontinued trastuzumab because of asymptomatic decreases in LVEF; 4% discontinued trastuzumab because of symptomatic cardiotoxicity. While the sequential use of trastuzumab following anthracycline administration is increasingly accepted, many clinicians feel that the concomitant use of this combination increases the risk sufficiently so that such regimens should not be routinely implemented.

There have been inconsistent reports of high incidence of cardiotoxicity with combinations of conventional doxorubicin and paclitaxel (AT) (Gianni et al 1995; Dombernowsky et al 1996; Moore et al 1998; Valagussa et al 2001). In the trials with the highest incidence of cardiotoxicity, paclitaxel was given as a 1- or 3-hour infusion in close approximation to the administration of conventional doxorubicin as a bolus or short infusion. The incidence of cardiomyopathy was relatively

small as long as the cumulative dose of conventional doxorubicin in combination with paclitaxel was less than 360 mg/m^2. Cardiotoxicity from the AT combination was first reported from a trial in which 35 women with breast cancer received conventional doxorubicin 60 mg/m^2 15 minutes before or after escalating doses of paclitaxel 125–200 mg/m^2. Five-year follow-up of 141 patients from this trial and 2 other similar trials identified 7 cases of CHF (5%): 1 case after a cumulative conventional doxorubicin dose of 120 mg/m^2 and 6 after 360 mg/m^2 (Valagussa et al 2001). Another 11 patients had LVEFs of $<$50% that returned to normal with longer follow-up. The actuarial cumulative risk of CHF was 30% overall, but was only 4% in those who received less than 360 mg/m^2 of conventional doxorubicin.

This increased risk of cardiotoxicity with the combination therapy may be attributable to the pharmacokinetic interference between paclitaxel and doxorubicin which may result in nonlinear plasma disposition of doxorubicin and increased plasma concentrations of doxorubicin and doxorubicinol (Gianni et al 1997). In a retrospective analysis of 657 patients treated with AT in 10 trials performed at multiple centers, 4.7% developed CHF (Gianni et al 2001), although the incidence of CHF in the patients treated with AT was not very different from that of a single-agent conventional doxorubicin at cumulative doses below 340–380 mg/m^2.

Mechanism of cardiac-sparing effect of liposomal anthracyclines

Nonpegylated liposomes generally extravasate in areas of pathology where capillaries are disrupted by inflammation or tumor growth and in organs lined with fenestrated endothelial barriers (ones without tight junctions such as the liver, spleen, and bone marrow) (Gabizon et al 1997; Schiffelers et al 2000). Since the myocardium is supplied by vessels with tight junctions (Tardi et al 1996), liposomal encapsulation would be expected to shift doxorubicin away from myocardial tissue, while maintaining tumor exposure. This tissue distribution pattern is supported by various preclinical and clinical pharmacologic studies of class I to III liposomal doxorubicin formulations summarized here, although the rapid clearance by the reticuloendothelial system of these early generations of liposome formulations may reduce the liposome fraction deposited in the tumor. Furthermore, pegylated liposomal doxorubicin (PLD) is preferentially taken up by tumor compared with normal cells in patients with breast and other solid cancers.

Encapsulation of doxorubicin by pegylated liposomes, causes impairment of its uptake by the reticulo-endothelial system, which results in the prolongation of the serum half-life to around 50 hours compared with 10 minutes for the free drug (Berry et al 1998). Due to an additional polyethylene glycol layer, the PLD also has lower uptake by the mononuclear phagocyte system, resulting in a greater plasma half-life relative to other liposomal anthracyclines. As a result, pegylated liposome formulations remain in circulation to a much longer extent, entering tumors through the leaky tumor vasculature in high levels, and to a much lesser extent in normal tissues outside the reticuloendothelial system (Gabizon et al 2003). Indeed, drug levels measured in heart muscle after correction for blood content are lower for PLD than for conventional doxorubicin, more so when peak concentrations are compared (Papahadjopoulos et al 1991). Moreover, because the interstitial spaces in the myocardium are well drained by lymphatics (Eliskova and Eliska 1989), much of the drug carried into this compartment by extravasated liposomes may pass through the tissue spaces and enter lymphatic flow in encapsulated form without releasing doxorubicin. Drug remaining encapsulated while passing through the myocardium would not become bioavailable and thus would not be expected to contribute to cardiac muscle cell toxicity. Another likely mechanism by which liposomal doxorubicin may attenuate cardiotoxicity is simply by blunting the high plasma peak levels of free drug associated with bolus injections of conventional doxorubicin that correlate with cardiotoxicity (Lyass et al 2000).

Monitoring cardiotoxicity

Cardiotoxicity of conventional doxorubicin remains a real issue despite the introduction of cardioprotectants. Liposomal formulations have reduced these concerns with regard to the treatment of some forms of malignancy; this is especially true with regard to ovarian and breast cancer (O'Brien et al 2004; Mrozek et al 2005). Because of the significant heterogeneity of anthracycline toxicity, monitoring for early detection before the clinical onset of cardiomyopathy is of paramount importance in the management of patients receiving anthracycline based chemotherapy. This may lead to appropriate intervention when the need arises (Ewer et al 2005).

Endomyocardial biopsy

Billingham et al (1978) developed a histologic scoring system based on endomyocardial biopsy that displays higher sensitivity for early cardiac damage and has shown good correlation with the cumulative dose of anthracyclines (Table 2). However, it is an invasive test with its attendant morbidity-thus making it impractical for day to day monitoring. The histologic changes do not correlate with subsequent risk of

CHF, neither does it provide data on myocardial function or the clinical state of the patient. Therefore, although traditionally considered as the "gold standard" test for the evaluation of anthracycline cardiomyopathy, other tests like radionuclide ventriculography or echocardiography are used more commonly in the evaluation of cardiotoxicity.

Radionuclide ventriculography (RNVG)

A retrospective series, reviewed by Schwartz et al (Schwartz et al 1987) on 1487 doxorubicin-treated patients investigated over a 7-year interval using RNVG suggests that serial RNVG is an appropriate and cost-effective approach for the prediction and prevention of impending CHF. Assessment of serial LVEF and assessment of regional wall motion by RNVG are now an integral part of monitoring cardiotoxicity. This accurate and highly reproducible test identifies high risk patients for developing doxorubicin cardiomyopathy including: (1) those with a decline of more than 10 ejection fraction percentage points from normal baseline to a final value of less than 50%; (2) those with a baseline ejection fraction of less than 50%. or (3) those receiving a total doxorubicin dose of 450 mg/m^2.

2D-echocardiography

This is a completely noninvasive test, highly portable, does not utilize ionizing radiation, and is readily available. Although extensively used in clinical practice, monitoring changes in systolic function alone has not achieved the desired goal of early detection of subclinical cardiac damage. In addition to the parameters measured by RNVG (systolic function and wall motion) echocardiography also incorporates the diastolic function which some consider to be a more accurate predictor of early cardiotoxicity (Stoddard et al 1992; Ganz et al 1993) possibly allowing a modification of treatment strategies to protect the vulnerable myocardium. Indeed, such pre-emptive treatment could contribute to a significant reduction in chemotherapy related cardiotoxicity. Complete details regarding the methods of performing these tests are beyond the scope of this review.

Antimyosin antibody scintigraphy

Radio labeled antimyosin antibody scintigraphy is a very sensitive test for the monitoring of anthracycline cardiotoxicity. The myocardial uptake of antimyosin antibody is highly correlated with the severity of myocardial injury. In fact at a cumulative dose of 240–300 mg/m^2 doxorubicin, almost all patients will exhibit a positive result (Valdes Olmos et al 2002) making it an impractical test to be applied and interpreted routinely.

Biomarkers for detection of cardiotoxicity

Troponin levels correlate well with histologic changes related to early cardiomyocyte damage in acute myocardial infarction (Jaffe et al 2006). Similarly, monitoring with brain natriuretic peptides (BNP) has been used to monitor patients with CHF (Price et al 2006). However, notwithstanding some indication that these markers are elevated in patients who have experienced anthracycline exposure, the tests, as utilized at this time neither have the sensitivity nor specificity to clearly predict a subgroup of patients that either should avoid these agents or who should have alternate forms of cardiac monitoring (Nousiainen et al 1999; Gaze and Collinson 2005; Polena et al 2005). Additionally, troponins and BNP may be elevated in the cancer patient for reasons that have not yet been fully elucidated, or to conditions that occur more frequently in the cancer patient such as ischemic heart disease (Jaffe et al 2006), pulmonary embolism (Tulevski et al 2006), and sepsis (Favory and Neviere 2006).

Strategies to minimize cardiotoxicity

Strategies to minimize cardiotoxicity include the use of protective agents such as dexrazoxane (Silber 2004), different preparations of anthracyclines, and alternative scheduling techniques. Readers are referred to the previous reviews where these have been described in details (Iarussi et al 2001). Liposomal formulations of conventional doxorubicin represent one of the recent approaches to ameliorating and or preventing the problem of anthracycline cardiotoxicity.

Liposomal anthracyclines

There are various formulations of liposomal anthracyclines for human use, including liposomal daunorubicin (DaunoXome®), liposomal doxorubicin (D-99, Myocet®), and PLD (Doxil® and Caelyx®). However, all conventional or pegylated liposomes are not the same. The ratio and the composition of various lipids can be modified for different liposomal compounds and the percentage of polyethylene glycol (PEG) added to the liposome can also be different, yielding varied pharmacodynamic properties.

The introduction of targeted therapy in addition to conventional chemotherapy for the management for various cancers has improved the outlook for patients. More and more methodology is being devised to provide relatively safer drugs. One such technique is the encapsulation of doxorubicin in PEG-coated liposomes (Vail et al 2004). Liposomes are microscopic vesicles consisting of a phospholipid bilayer that when placed around an active drug alters the pharmacologic

and pharmacokinetic profiles of conventional anthracycline. To protect the molecule further from phagocytosis, a polyethylene glycol (PEG) coating may be used around the liposome bilayer by a process known as pegylation, and the new compound is called a pegylated liposomal anthracycline. Another rationale of encapsulating doxorubicin within liposomes is to allow the sequestration of the drug from organs such as the heart and gastrointestinal tract that have tight capillary junctions, while enhancing delivery of the cytotoxic agent to tumor sites lined by compromised vasculature (Hobbs et al 1998). As such the drug delivery to the tumor is enhanced, it results in increased concentration of the drug at the tumor site. This also confers a longer half-life, smaller volume of distribution, and reduced clearance of the drug at the tumor site, all resulting in a greater efficacy (Allen and Martin 2004). On the basis of these pharmacokinetic principles alone, liposomal doxorubicin has potential applications to treat a variety of cancers either alone or as part of combination therapy (Vaage et al 1994).

Conventional doxorubicin enters tissues as a concentrated pulse. Pegylated liposomes, on the other hand, cause doxorubicin to be slowly released into these tissues over several days, and change the biodistribution of the drug away from normal tissues. Thus the proportion of doxorubicin that is bioavailable at the tumor site at any one time is several times higher than it is in normal tissues (Vaage et al 1994). Since only the free doxorubicin that is released from the liposome is bioavailable doxorubicin concentration does not exceed that of conventional doxorubicin except in the sites with extensive reticuloendothelial systems where intact liposomes accumulate (Vaage et al 1994; Hobbs et al 1998; Allen and Martin 2004; Vail et al 2004). Since doxorubicin in the plasma remains encapsulated in liposomes, the plasma level of free doxorubicin that is responsible for toxicity of non-tumor related organs including the myocardium remains very low following administration of PLD. Thus, toxicity normally associated with conventional doxorubicin is significantly decreased. A detailed review of the structure, pharmacokinetic, and pharmacodynamics of these agents have been discussed elsewhere (Vail et al 2004), and is beyond the scope of this review. Moreover, prolonged half-life and targeted delivery to the tumor makes it possible to use less frequent dosing without diminishing the efficacy, thereby potentially enhancing tolerability and convenience of therapy (Vaage et al 1994).

Preclinical treatment models of PLD

PLD and other pegylated liposomal formulations of anthracycline have been evaluated in numerous animal models. In preclinical models, pegylated liposomal formulations that differ either in the lipid make-up of the liposome or the amount of PEG on the surface of the liposome, were shown to be equally effective against low- and high-growth fraction tumors (Vail et al 2004). It resulted in remission and cure against a wide variety of solid cancers including malignancies of the breast, lung, ovaries, prostate, colon, bladder, and pancreas, as well as against hematologic malignancies including lymphoma, and myeloma (Gabizon et al 2006). As adjuvant therapy, it was also noted to be equally effective. Additionally, liposomal anthracyclines cross the blood-brain barrier to induce remission in malignancies of the central nervous system (Saito et al 2004). It also showed additive and synergistic effects when used in combination with vincristine or trastuzumab (Bernard-Marty et al 2006). An interaction between the liposome and P-glycoprotein function, as well as increased concentrations at tumor site, might even overcome multidrug resistance in selected cases. Several investigations are underway following these studies which provided preliminary evidence of its many potential uses. A summary of some of the more important preclinical data follows.

Colon cancer

Tumor burden of doxorubicin-resistant C26 mouse colon cancer in Balb/c male mice treated with PLD was markedly inhibited as opposed to no significant inhibition of tumor growth with conventional doxorubicin on days 10, 17, and 24 after tumor inoculation (Mayhew et al 1990; Huang et al 1992).

Breast cancer

PLD is more effective at inhibiting the growth of xenografts initiated by subcutaneous inoculation of BT474 and MDA MB453 human breast cancer cell lines or primary human breast cancer, B585, in nude mice compared with the same dose or a higher dose of conventional doxorubicin (Colbern et al 1998). PLD treatment also significantly increased the mean survival time of mice with MC2 and MC65 tumors, 8 weeks after tumor implantation (Vaage et al 1992).

Ovarian and other cancers

Similar anti-tumor activity of PLD and significant increases in mean survival time were also evident in nude mice implanted either subcutaneously or intraperitoneally (IP) with the human ovarian carcinoma HEY (Vaage et al 1993), lung cancer (Colbern et al 1999), leukemia (Working and Dayan 1996), lymphoma (Cabanes et al 1998), and in prostate cancer (Vaage et al 1994). However, PLD did not perform as well as

conventional doxorubicin in orthotopic xenografts of human bladder cancer (Mazurchuk et al 1997).

Cardiotoxicity in preclinical trials

In general, toxicities observed in animals with PLD treatment are similar to but less severe than those of conventional doxorubicin with several important exceptions, most notably cardiotoxicity (Working and Dayan 1996). At identical cumulative doses of conventional doxorubicin, both the incidence and severity of cardiotoxicity were either substantially decreased or entirely absent in rats, rabbits, and dogs administered PLD (Vaage et al 1994; Cabanes et al 1998). The decreased cardiotoxicity may be related to the decreased peak concentration of free, non-liposomal doxorubicin in the plasma and tissues of PLD-treated animals.

Preclinical studies

In preclinical studies, liposomal formulations have been classified in different ways depending on the lipid make-up of the liposome or the amount of PEG on the surface of the liposome; they have been classified as classes I–IV.

Class Ia/Ib liposomal doxorubicin

Rahman and colleagues have extensively studied the pharmacological, toxicological, and therapeutic effects doxorubicin entrapped in cardiolipin liposomes including comparing cardiotoxicity of a type Ia liposomal doxorubicin with that of conventional doxorubicin in groups of mice (Rahman et al 1980, 1982, 1984, 1985; Herman et al 1983). At a dose of 4 mg/kg, the peak cardiac concentration achieved in 30 minutes following conventional doxorubicin administration was significantly higher than that with the drug entrapped in cardiolipin liposomes, resulting in a significantly lower histopathologic lesions in cardiac tissue of mice as determined by electron microscopy (Rahman et al 1980, 1984, 1985; Herman et al 1983). Gokhale et al (1996) reported an improved formulation using synthetic cardiolipin in 1996 – class Ib – which despite achieving a 44-fold higher plasma drug levels showed levels in cardiac tissue at least 2-fold lower than that observed with conventional doxorubicin in mice.

Class II liposomal doxorubicin

In one representative study of the class II liposomal doxorubicin formulation, the cardiac toxicity of conventional doxorubicin was compared with that of doxorubicin encapsulated in liposomes incorporating phosphatidylcholine, phosphatidylserine, both negatively charged, naturally occurring phospholipids, and cholesterol (Storm et al 1989). After 5 daily doses of 2.0 mg/kg, a much lower doxorubicin concentration was found in cardiac tissue with the administration of the class II liposomal formulation relative to conventional doxorubicin given either by bolus or infusion. Other studies of class II liposomal formulations supported these observations (Gabizon et al 1982, 1983, 1986). The histopathology scores of myocardial lesions based on the method of Bertazzoli et al (Solcia et al 1981) were significantly lower for liposomal doxorubicin. Moreover, there was a trend to improvement in the off-therapy period in the liposomal doxorubicin treated groups.

Class III liposomal doxorubicin

Preclinical studies showed that administration of class III doxorubicin liposomes reduces the peak distribution of the drug to the heart but effectively delivers doxorubicin to tumors (Balazsovits et al 1989; Kanter et al 1993). None of the dogs treated with non-PLD (NPLD) had lesions suggestive of cardiomyopathy compared to moderate to severe vacuolization of myocardial tissue in those that received conventional doxorubicin.

Class IV PLD

Dogs treated with conventional doxorubicin up to a cumulative dose of 10 mg/kg showed vacuolization and myofibrillar loss in the myocardium, while no histologic evidence of cardiotoxicity was seen in dogs exposed to PLD (Working et al 1999) either 1 or 5 weeks after treatment. In rabbits, progressive cardiomyopathy was seen in both conventional and liposomal doxorubicin treatment groups, but the cardiomyopathy was more frequent and severe with conventional doxorubicin than with PLD.

Clinical trials with liposomal anthracyclines

Class I and II liposomal doxorubicin

In a phase II clinical study 20 patients with advanced breast cancer were treated with class Ia liposome-encapsulated doxorubicin with a cumulative dose greater than 500 mg/m^2. Five of these 20 underwent endomyocardial biopsies 4 demonstrating no histologic change (Billingham grade 0) and 1 showing mild myofibrillar loss and dilatation of the sarcoplasmic reticulum involving less than 5% of cardiac myocytes in. The cumulative dosage for these patients was up to 750 mg/m^2. Even those who had decreases in LVEF (2) had no clinical evidence of CHF and a Billingham

endomyocardial biopsy score of 0.9. Class II liposomal doxorubicin formulations were used in two pilot clinical trials but the cumulative doses were too low to assess cardiotoxicity (Gabizon et al 1989; Owen et al 1992).

Class III liposomal doxorubicin

The first of several large randomized trials involved 224 women with metastatic breast cancer exposed to equal dosages and schedule of NPLD or conventional doxorubicin (Harris et al 2002). There was a significant difference in favor of the NLPD in the percentage of patients with protocol-defined cardiotoxicity and the number of patients with CHF despite similar efficacy of the regimens. The hazard ratio for cardiotoxicity with conventional doxorubicin compared with NPLD was 3.56 ($p = 0.0001$) (Figure 2A). Cardiac biopsies in 36 of these patients documented a Billingham score >2.5 in 70% of the patients treated with conventional doxorubicin compared to 5% of the patients treated with NPLD (FDA 2002).

Cardiotoxicity findings of a randomized clinical trial in patients with breast cancer using NPLD in combination with cyclophosphamide 600 mg/m^2 every 3 weeks (MC regimen) (Batist et al 2001) were compared with the same doses in the conventional doxorubicin plus cyclophosphamide regimen (AC regimen). The efficacy of the two combinations was similar but protocol-defined cardiotoxicity was significantly less common with the MC regimen. Patients were 80% less likely to develop cardiotoxicity while on MC compared with AC (hazard ratio 4.8) and the time to a cardiac event was significantly longer for MC treatment (Figure 2B). There was a gradual decrease in median LVEF as the cumulative dose of NPLD increased, but this too was less marked than was seen with conventional doxorubicin. In another study, no significant differences were noted in the incidence of cardiotoxicity between patients treated with NPLD 75 mg/m^2 plus cyclophosphamide 600 mg/m^2 when compared with the same doses of epirubicin and cyclophosphamide. Taken together, the randomized trials comparing similar doses of NPLD and conventional doxorubicin, either alone or in combination, provide strong evidence for the principle that liposomal encapsulation of conventional doxorubicin results in a substantial reduction, but not total eradication, of cardiotoxicity (Batist et al 2000).

Anthracyclines in high risk cardiac patients

In a subset analyses in 68 high risk cardiac patients (because of either prior conventional doxorubicin exposure or other risk factors for cardiac disease) performed on pooled data from the randomized trials (Batist et al 2000; Winer et al 2000), predefined cardiotoxicity was documented in 22% of the patients receiving NPLD and 39% receiving conventional doxorubicin despite being exposed to a greater cumulative anthracycline dose on the NPLD arm (median, 308 mg/m^2; $n = 32$) than the conventional doxorubicin arm (median, 225 mg/m^2; $n = 36$). CHF was seen in 3% and 8%, respectively and the cumulative anthracycline dose before a cardiac event was 780 and 570 mg/m^2 ($p = 0.001$) for NPLD and conventional doxorubicin. Using the same database, Winer et al (2000) looked at a subset of patients at increased risk of cardiotoxicity as a consequence of age (mean 65 years), prior mediastinal/chest irradiation, prior adjuvant conventional doxorubicin (240 mg/m^2) or prior cardiac disease (Winer et al 2000). Cardiotoxicity occurred in 10% of those who received NPLD and 26% of those who received conventional doxorubicin ($p = 0.003$). CHF was seen in 1% and 7% and the cumulative lifetime doxorubicin dose was 785 and 570 mg/m^2 ($p = 0.0001$) respectively in the NPLD and conventional doxorubicin arms (Winer et al 2000).

NPLD: combinations with other cardiotoxic agents

In addition to cumulative-dose concerns, the cardiotoxicity of conventional anthracyclines is enhanced by coadministration of other cardiotoxic agents such as paclitaxel or trastuzumab. However, several small phase I/II trials assessed the efficacy and safety profile, including the risk for cardiac toxicity, of NPLD in combination with cardiotoxic agents. Overall, the combination of conventional doxorubicin and trastuzumab results in significantly greater cardiotoxicity than the same cumulative dose of conventional doxorubicin alone (Slamon et al 2001; Theodoulou et al 2002; Trigo et al 2002). However, until a randomized trial has been completed it will be difficult to determine how the safety and efficacy of NPLD plus trastuzumab compare with those of conventional doxorubicin and trastuzumab.

NPLD: dose intensification

The reduced cardiotoxicity from NPLD could lead to either prolonged duration of administration with higher cumulative lifetime doses or reduced toxicity on dose escalation. In two studies that have addressed the latter, no evidence of clinical cardiotoxicity was observed (Moore et al 1998), but no added therapeutic benefit to the dose escalation was seen (Shapiro et al 1999).

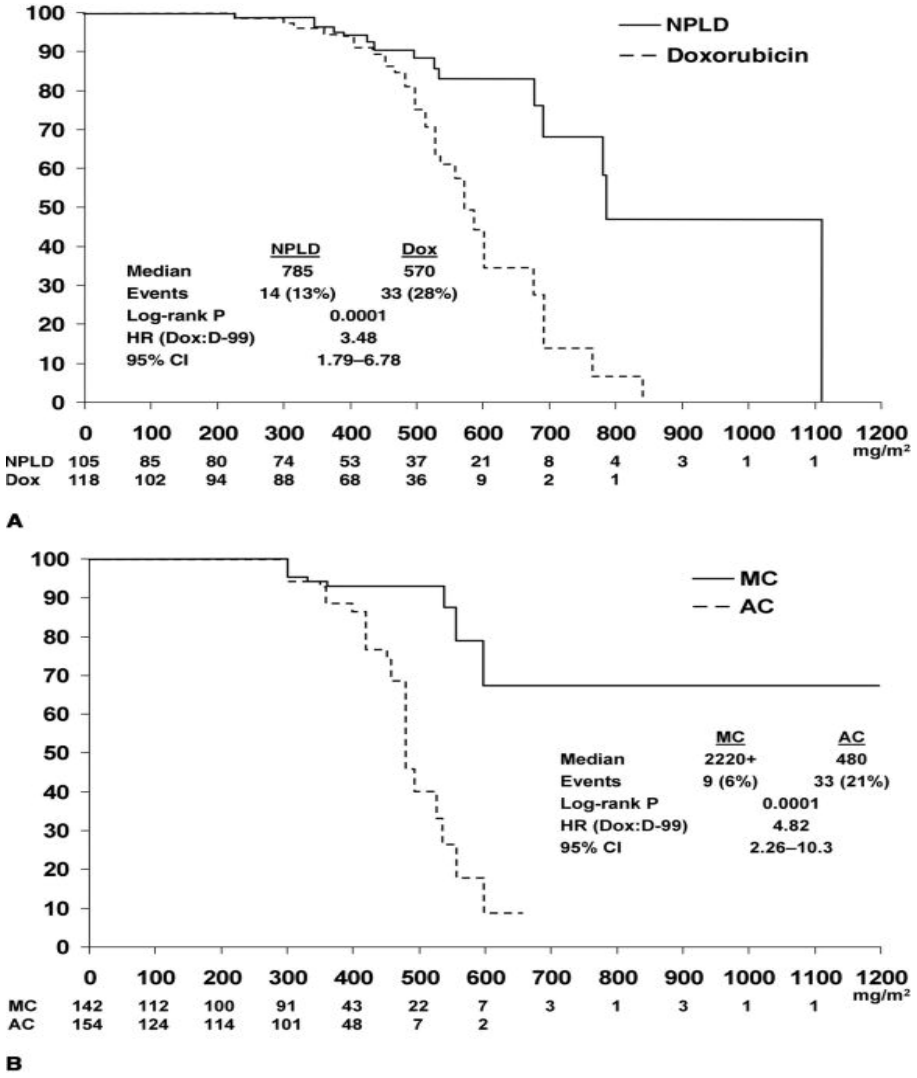

Figure 2 Cumulative time to a cardiotoxicity endpoint, defined as a decrease in LVEF by more than 20 units to a value >50%, a decrease in LVEF by more than 10 units to a value <50%, or CHF. (**A**) Patients who received either NPLD alone or conventional doxorubicin alone (Dox) in a dose of 75 mg/m^2 every 3 weeks. From Harris L, Batist G, Belt R, et al 2002. Liposome-encapsulated doxorubicin compared with conventional doxorubicin in a randomized multicenter trial as first-line therapy of metastatic breast carcinoma. *Cancer*, 94:25–36. Copyright © 2002 American Cancer Society. This material is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc. (**B**) Patients who received cyclophosphamide 600 mg/m^2 every 3 weeks plus either NPLD (MC) or conventional doxorubicin (AC) in a dose of 60 mg/m^2 every 3 weeks. Reprinted with permission from Batist G, Ramakrishnan G, Rao CS, et al 2001. Reduced cardiotoxicity and preserved antitumor efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized, multicenter trial of metastatic breast cancer. *J Clin Oncol*, 19:1444–54. Copyright © 2001 American Society of Clinical Oncology.

Class IV PLD

Myocardial tissue was evaluated for evidence of anthracycline-induced cardiac damage in 10 patients with AIDS-related KS who had received PLD to cumulative doses of 440 to 840 mg/m^2, and blinded endomyocardial biopsy scores were compared with two control groups. PLD-treated patients had lower biopsy scores than conventional doxorubicin-treated patients despite receiving higher cumulative doses of anthracycline. Median biopsy scores were 0.3 for PLD, 3.0 for conventional doxorubicin control group 1 ($p = 0.002$ vs PLD), and 1.25 for conventional doxorubicin control group 2 ($p < 0.001$ vs PLD) (Berry et al 1998).

In another study of 5 AIDS patients, when the cumulative doses ranged from 1680 mg/m^2 to 2360 mg/m^2, LVEF on echocardiography fell below normal in only one patient, and this change was not correlated with clinical manifestations of a cardiomyopathy (Mustafa 2001).

PLD: cardiac function in studies of solid tumors

In a retrospective analysis of 237 patients from 8 phase I/II trials of PLD therapy 42 reached or exceeded cumulative doses of 500 mg/m^2 (range, 500–1500 mg/m^2); serial multiple-gated acquisition (MUGA) scans were available

for 41 patients: 5 (12%) had >10% decrease in LVEF, but no patient had clinical CHF secondary to cardiomyopathy (Safra et al 2000). Six patients, including 3 who had received conventional doxorubicin previously, underwent endomyocardial biopsies after cumulative doses of 490–1320 mg/m^2. In five patients, Billingham endomyocardial biopsy scores ranged from 0 to 1, while the sixth had a score of 1.5 after both 900 and 1320 mg/m^2 of PLD. Of the 195 patients who received cumulative PLD doses less than 500 mg/m^2, one episode of CHF was recorded in a 70-year-old woman who had previously received chest irradiation and mitoxantrone exceeding a cumulative dose of 120 mg/m^2.

Results of 10 endomyocardial biopsies in 8 patients treated with cumulative anthracycline doses greater than 550 mg/m^2, including more than 400 mg/m^2 of PLD have been reported (Gabizon et al 2004). The median dose for cumulative anthracycline exposure was 908.5 mg/m^2 (range, 498–1680 mg/m^2) and the median cumulative PLD dose was 707.5 mg/m^2 (range, 490–1485 mg/m^2). In spite of high cumulative doses of PLD and, in some cases, prior treatment with conventional doxorubicin, endomyocardial biopsy scores showed very limited damage relative to what would be expected from similar cumulative doses of conventional doxorubicin alone (Wolf 2001).

In retrospective studies of patients with gynecologic cancers, maintenance PLD treatment in 18 patients with recurrent malignancy showed no clinical cardiac dysfunction; no changes in LVEF or symptomatic CHF were seen (Muggia et al 2004; Uyar et al 2004). Cardiac function was systematically evaluated as part of a pivotal randomized trial in which 474 patients with advanced ovarian cancer received either PLD 50 mg/m^2 every 4 weeks or topotecan (Gordon et al 2001). No patient on either arm of the study developed CHF. At the time of the most recent report of results from this trial, 132 of the PLD-treated patients had both a baseline and at least one subsequent LVEF assessment; 61 of these patients received cumulative PLD doses in excess of 300 mg/m^2 and 14 received more than 450 mg/m^2 (highest cumulative dose = 1301 mg/m^2) Three of the 61 patients showed a >20% absolute decrease in LVEF from baseline and three had at least one follow-up LVEF <45% (two of whom began the study with LVEF <45%). None of these patients showed clinical signs or symptoms of CHF and there was no evidence of a relationship between cumulative PLD dose and change from baseline LVEF.

In another randomized trial, 301 patients with metastatic breast cancer of whom 83% had received conventional anthracyclines previously and 37% were considered resistant to anthracycline therapy were evaluated (Keller et al 2004). The lifetime cumulative dose of anthracycline exceeded 450 mg/m^2 in 34 patients and exceeded 600 mg/m^2 in 14 patients on the PLD arm. Twenty-two of the PLD-treated patients met one or both criteria for LVEF change from baseline, but none of the patients developed signs or symptoms of CHF. Eight of these 22 patients had received a cumulative anthracycline dose >450 mg/m^2 (pretreatment anthracycline plus PLD). Only one patient discontinued PLD treatment because of a decrease in LVEF, but it was not clear that this was related to PLD in part because the cumulative lifetime anthracycline dose was only 199 mg/m^2.

Cardiac toxicity from PLD has been compared with conventional doxorubicin in two randomized trials. A randomized trial directly comparing PLD and conventional doxorubicin was attempted but discontinued early because of excessive cardiotoxicity in the conventional doxorubicin arm (Moore et al 1998). The overall response rates were 70% to conventional doxorubicin/paclitaxel and 69% to PLD/paclitaxel. None of the patients who received PLD/paclitaxel had cardiotoxicity. Six of the 10 patients given conventional doxorubicin developed cardiotoxicity with reduction in LVEF from 60% at the end of the last cycle of chemotherapy to 10% 3 weeks later. Cardiac function remained abnormal for the remainder of the lives of 2 patients. Variable cardiac toxicity (grade 1–3) was noted in the other four patients. In another trial, 509 patients with metastatic breast cancer were randomly assigned to receive either PLD 50 mg/m^2 every 4 weeks or conventional doxorubicin 60 mg/m^2 every 3 weeks (O'Brien et al 2004). There were no significant differences in cardiac event-free survival between the PLD and conventional doxorubicin groups. However, 16% of patients continued PLD treatment for more than 9 months, compared with only 1% of patients receiving conventional doxorubicin. Ten patients (4%) on the PLD arm and 48 patients (19%) on the conventional doxorubicin arm developed cardiotoxicity. Of these patients, none on the PLD arm and 10 (4%) on the conventional doxorubicin arm had signs or symptoms of CHF. The likelihood of experiencing a cardiac event was 3.2 times greater on the conventional doxorubicin arm ($p = 0.0006$) (Figure 3). PLD was also significantly less cardiotoxic than conventional doxorubicin among patients who had received prior anthracycline treatment and those who had a cardiac risk factor at baseline. Despite the differences in dose and schedule of the two anthracycline formulations, this study suggested that patients can be treated for longer periods with PLD with less risk of cardiotoxicity and similar progression-free survival (O'Brien et al 2004).

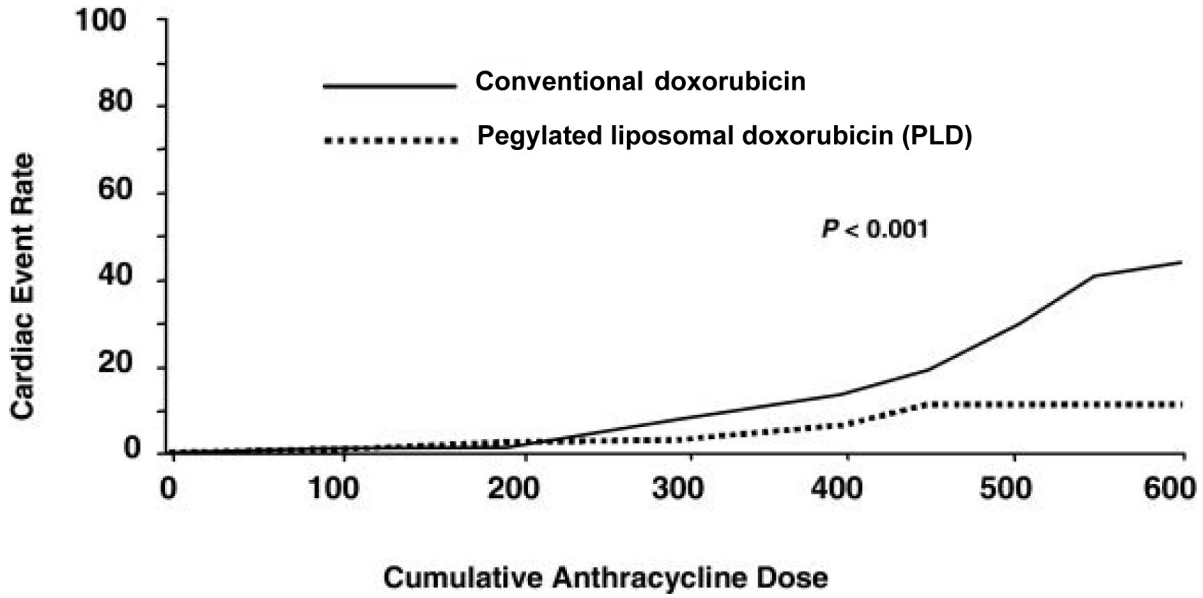

Figure 3 Cardiac event-free survival for PLD versus conventional doxorubicin in a randomized comparison of 509 patients with metastatic breast cancer. Cardiac event was defined as a decrease in LVEF by more than 20 units to a normal value, a decrease in LVEF by more than 10 units to an abnormal value, or CHF Patients received either PLD 50 mg/m^2 every 4 weeks or conventional doxorubicin 60 mg/m^2 every 3 weeks. The cumulative anthracycline dose included exposure before entry onto trial plus the total amount received during the course of the study. Adapted with permission from O'Brien ME, Wigler N, Inbar M, 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,* 15:440–9. Copyright © 2004 Oxford University Press.

PLD in combination with other cardiotoxic drugs

Early results of clinical trials suggest that combining trastuzumab or a taxane with PLD significantly reduces cardiotoxicity risk without reducing chemotherapeutic efficacy. In a nonrandomized trial by the Eastern Cooperative Oncology Group (ECOG 3198) the cardiac safety of PLD plus docetaxel, with or without trastuzumab, was evaluated in patients with HER2/neu-negative tumors and in patients with tumors that overexpressed HER2/neu. The addition of trastuzumab to PLD and docetaxel did not appear to increase the risk of cardiotoxicity as no cases of CHF were reported on either treatment arm. In a separate phase II trial in 30 patients with HER2-positive metastatic breast cancer (Chia et al 2006) receiving PLD 50 mg/m^2 every 4 weeks and trastuzumab (4 mg/kg loading dose then 2 mg/kg weekly) only 3 patients experienced protocol-defined cardiotoxicity, all had received prior anthracyclines, but no patient had symptomatic CHF. However, demonstration that the combination of PLD with trastuzumab is safer than conventional doxorubicin plus trastuzumab must await completion of these ongoing studies.

Liposomal daunorubicin

Conflicting results emerged from clinical trials evaluating cardiac safety of liposomal daunorubicin. A randomized clinical trial of KS included 116 patients who received DNX 40 mg/m^2 every 2 weeks (Gill et al 1996) no cases of LVEF decline >20% was demonstrated on total of 115 repeat LVEF determinations. However, in a phase I study of patients with metastatic breast cancer, 1 in 5 patients experienced asymptomatic cardiotoxicity with >15% decline in baseline LVEF at cumulative DNX doses of 800, 960, and 600 mg/m^2 (plus 300 mg/m^2 of adjuvant conventional doxorubicin therapy) (O'Byrne et al 2002). In another study of 122 patients, 2 patients who received DNX 150 mg/m^2 (1 with a cumulative dose of 900 mg/m^2) experienced cardiotoxicity and died. During 6 months of follow-up in 14 patients, LVEF fell below 45% in one patient. The cardiotoxicity was more problematic with pediatric malignancies. In 14 children with recurrent or progressive brain tumor, DNX therapy (up to 600 mg/m^2 total) was associated with slight cardiotoxicity in three patients (21%) and a mean overall decrease of 13.8% in LVEF (Lippens 1999). A subsequent phase I study of 48 children 1–18 years old was not completed because of evidence of cumulative cardiac toxicity (Lowis et al 2002). Thus while long-term cardiac safety studies with DNX are not available, in the short term cardiotoxicity may limit the usefulness of DNX.

Conclusion

Encapsulating conventional doxorubicin into pegylated liposomes has opened new avenues of study for improvement of cancer treatment without a concomitant increase in toxicity. The liposomal components of PLD change the basic

pharmacology and pharmacokinetics of the conventional doxorubicin it encapsulates. These changes effectively allow PLD to travel to and concentrate in tumors without excess exposure of normal cells, thus raising the therapeutic index for conventional doxorubicin delivered in this manner. These attributes are reflected in data from numerous preclinical studies, providing proof of principle that pegylated liposome-encapsulated cytotoxic drugs, either alone or as part of combination therapy, have a variety of potential applications in the treatment of cancers. The limited available clinical evidence suggests that liposomal anthracyclines can be used in place of conventional anthracyclines to reduce the risk of cardiotoxicity without reducing the efficacy of therapy in the treatment of some malignancies. Further results are eagerly awaited from ongoing controlled trials of cardiac safety with long-term liposomal anthracycline therapy, either alone or in combination with cardiotoxic agents.

Similarly, future developments in the rapidly evolving field of pharmacogenomics are likely to permit oncologists to tailor therapy to optimize therapeutic effectiveness, while minimizing toxicity. There are genuine reasons to be enthusiastic. Further, it can be anticipated that our growing understanding of the critical role of specific molecular events in individual cancers will permit the development of prognostic and, most importantly, predictive biomarkers, which will aid in the selection of optimal management strategies for individual patients. In addition, it is important to continue to aggressively explore innovative methods of using established cytotoxic agents such as regional treatment, maintenance therapy, weekly/daily delivery schedules, and concurrent chemotherapy-radiation therapy.

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