review

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Expert opinion on the use of anthracyclines in patients with advanced breast cancer at cardiac risk

P. J. Barrett-Lee[1]*, J. M. Dixon[2], C. Farrell[3], A. Jones[4], R. Leonard[5], N. Murray[6], C. Palmieri[7], C. J. Plummer[8], A. Stanley[9] & M. W. Verrill[10]

[1]Breast Unit, Velindre Cancer Centre, Cardiff; [2]Edinburgh Breast Unit, Western General Hospital, Edinburgh; [3]Breast Unit, Christie Hospital NHS Foundation Trust, Manchester; [4]Department of Oncology and Radiotherapy, Royal Free Hospital and University College Hospital, London; [5]Department of Medical Oncology, Imperial College Hospitals Trust, London; [6]Cancer Research UK Clinical Centre, University of Southampton, Southampton; [7]Department of Cancer Medicine, Imperial College London, London; [8]Department of Cardiology, Freeman Hospital, Newcastle Upon Tyne; [9]Department of Oncology, City Hospital, Birmingham; [10]Northern Centre for Cancer Treatment, Newcastle General Hospital, Newcastle Upon Tyne, UK

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Anthracyclines are considered to be among the most active agents for the treatment of breast cancer. However, their use is limited by cumulative, dose-related cardiotoxicity. Such cardiotoxicity results in a permanent loss of cardiac myocytes and a progressive reduction in cardiac function following each subsequent dose of anthracycline. Initially, damage to the heart is subclinical; however, increasingly impaired cardiac function can result in cardiovascular symptoms, with serious cardiac injury resulting in chronic heart failure. Since the early detection and treatment of cardiotoxicity can reduce its clinical effects, it is important that oncologists are aware of these adverse effects and manage them appropriately. This review examines the risk factors for anthracycline-associated cardiotoxicity and offers recommendations on strategies to reduce the cardiotoxicity of anthracyclines in the management of patients with advanced breast cancer.

Key words: advanced breast cancer, anthracyclines, cardiac monitoring, cardiotoxicity, liposomal anthracyclines, risk factors

introduction

Since their introduction in the 1960s, the anthracyclines, doxorubicin and epirubicin, have been considered to be among the most active agents for the treatment of breast cancer and are components of many adjuvant and palliative regimens [1]. Their clinical utility is, however, limited by cumulative, dose-related progressive myocardial damage that may lead to chronic heart failure (CHF), reduced quality of life, or death [2, 3]. Several other established and future chemotherapies for breast cancer are also known to have potentially important adverse effects on the cardiovascular system [4]. These include taxanes, alkylating agents (e.g. cisplatin), antimetabolites (e.g. capecitabine), and mitoxantrone as well as some of the newer targeted agents, such as trastuzumab, bevacizumab, and the tyrosine kinase inhibitor, sunitinib [4–7]. Radiation therapy to the chest has also been shown to have cardiotoxic effects [4]. Recently, there have been concerns that the use of aromatase inhibitors in breast cancer increases cardiovascular risk, especially as tamoxifen may protect against cardiovascular disease [8, 9]. As an increasing number of women survive breast cancer, the impact of cancer treatment on cardiovascular health is becoming ever more important. Since the early detection and treatment of cardiotoxicity can reduce its clinical effects, it is particularly important that oncologists are aware of these side-effects and manage them appropriately [10].

The sequential and concomitant use of adjuvant therapies, combined with other risk factors, such as age, obesity, and physical inactivity, may increase cardiovascular vulnerability and, ultimately, the risk of premature cardiovascular-associated mortality in patients with breast cancer—a phenomenon labelled the 'multiple-hit' hypothesis [4]. The consequences of the multiple-hit have important implications for the use of chemotherapy in women with advanced breast cancer [4, 11]. Although these patients may already be at an increased cardiac risk because of their adjuvant treatment or biological risk factors, they may still benefit from anthracycline therapy to treat their cancer. Since 50% of women who develop breast cancer are older than 61 years [12], it is important that clinicians are aware of preexisting co-morbidities and the short- and long-term cardiovascular effects that are associated with cancer treatments [13]. Several strategies have been developed to reduce anthracycline-induced cardiotoxicity; however, no consensus currently exists on optimal monitoring for associated adverse cardiac effects in patients with advanced breast cancer [14].

This paper reviews the key evidence and risk factors for anthracycline-associated cardiotoxicity and offers

Correspondence to: Prof. P. J. Barrett-Lee, Breast Unit, Velindre Cancer Centre, Whitchurch, Cardiff CF14 2TL, UK. Tel: 29 20615888 ext: 6384; Fax: 29 20196835; E-mail: peter.barrett-lee@velindre-tr.wales.nhs.uk

recommendations on strategies to reduce the cardiotoxicity of anthracyclines in the management of patients with advanced breast cancer. The recommendations are not intended to be prescriptive, but their aim is to help clinicians identify patients with advanced breast cancer at increased risk of cardiotoxicity, so that appropriate decisions regarding the use and monitoring of anthracycline therapy can be made.

search strategy and selection criteria

Data for this review were identified by searches of the Medline database using the search terms 'breast', 'carcinoma', 'cancer', 'cardiac*', 'heart', 'cardio*', 'cardiov*', 'cardiotox*', 'toxic*', 'chemotherapy*', 'anthracycline*', 'lifestyle', 'risk', 'behaviour*', 'comorbid*', and 'co-morbid*'. The search results were supplemented by manual searching of current journals, reference lists in key articles and other appropriate documents, and expert input.

All recommendations are based on the best available evidence supplemented by the authors' experiences in managing advanced breast cancer.

anthracycline cardiotoxicity

The cardiotoxicity of anthracyclines appears to be distinct from its therapeutic mechanism and has been attributed to multiple effects on cardiac myocytes, including apoptosis, alterations in iron homeostasis, deregulation of calcium homeostasis, and mitochondrial dysfunction [15]. The most comprehensively evaluated cardiotoxicity of doxorubicin is cumulative and dose-related progressive myocardial damage leading to clinical events, ranging from an asymptomatic reduction in left ventricular ejection fraction (LVEF) to irreversible life-threatening CHF [16]. Epirubicin is also associated with cardiotoxicity, although on a mg/mg basis is less cardiotoxic than doxorubicin, and can, therefore, be administered at higher cumulative doses (up to a total of ~900 mg/m^2 versus a total of 450 mg/m^2 for doxorubicin before cardiotoxicity limits further therapy). However, to achieve the same clinical benefit as doxorubicin, epirubicin tends to be given at 25–50% higher doses, which potentially negates the advantages of any higher cumulative dose threshold. Consistent with this, a recent a meta-analysis showed no evidence for a significant difference between the two anthracyclines in the occurrence of CHF [17].

classification of anthracycline toxicity

Anthracycline cardiotoxicity can be classified as acute, chronic, or late onset. In addition to clinical cardiotoxicity, manifesting itself as CHF, studies have reported subclinical cardiotoxicity. There is, however, a wide variation in the frequency of both clinical and subclinical cardiotoxicity after anthracycline therapy; furthermore, the clinical manifestation of cardiotoxicity can be diverse [15, 18] (Table 1).

Acute and subacute cardiotoxicity are rare. Acute cardiotoxicity is independent of the anthracycline dose; it is generally minor and reversible, ranging from asymptomatic electrocardiographic (ECG) changes to rare cases of severe acute myocarditis [19]. ECG changes can occur during or within several hours of the administration of an anthracycline.

Table 1. Clinical manifestation of anthracycline-induced cardiotoxicity [18]

Acute anthracycline cardiotoxicity
electrocardiographic changes
Arrhythmias
Pericarditis (infrequent)
Myocarditis (infrequent)
Subacute/chronic cardiotoxicity
Contractile dysfunction
Heart failure

These abnormalities rarely cause clinical symptoms and usually resolve spontaneously [20]. Cardiotoxicity that occurs soon after the administration of an anthracycline, however, maybe a harbinger of later toxicity [21].

Acute myocardial injury can be sensitively detected by measurement of plasma concentrations of cardiac troponin I (TnI), a contractile protein in the myocardium. As a result, an increase in TnI soon after high-dose chemotherapy is considered to be a strong indicator of left ventricular damage and poor cardiac outcome [22]. Furthermore, it can be used to predict, at a very early stage, the development of future ventricular dysfunction, as well as its severity [23].

Chronic or late onset anthracycline cardiotoxicity typically manifests months or years after chemotherapy and can lead to cardiomyopathy with a poor prognosis for affected patients. In a long-term prospective study of 120 patients with advanced breast cancer, those who received high cumulative doses of epirubicin (850–1000 mg/m^2) had a risk of CHF that increased over a 5-year period from 11% at 1 year to 14% and 20% after 2 and 5 years, respectively [24]. The true incidence of chronic cardiotoxicity is impossible to determine accurately because the follow-up time has been insufficient in most clinical trials [25].

anthracycline versus trastuzumab cardiac dysfunction

The anthracycline-associated abnormalities and their related cardiac insult represent an irreversible form of chemotherapy-related cardiac dysfunction (CRCD), referred to as type I CRCD [26]. By contrast, type II CRCD represents a profoundly different form of cardiac dysfunction. Type II CRCD, characterised by trastuzumab toxicity, is not dose related, does not appear to occur in all patients, and is not associated with any significant ultrastructural abnormalities. Furthermore, type II CRCD appears to be reversible, with a high likelihood of recovery, which type I is not [26].

risk factors associated with anthracycline cardiotoxicity

The best predictor of cardiotoxicity is the total cumulative dose of anthracycline [2, 27]. Ageing of the myocardium, preexisting cardiac dysfunction, long-standing hypertension, intercurrent cardiotoxic therapies, and prior irradiation therapy confer an

increased risk of cardiotoxicity, particularly when anthracyclines are given in high cumulative doses with bolus administration [28]. A greater understanding of these factors may help to reduce the occurrence and severity of cardiovascular side-effects [21].

treatment-related risk factors

cumulative dose of anthracycline. Extensive analyses have shown a direct relation between the occurrence of heart failure and the cumulative anthracycline dose [27] (Table 2). The probability of developing CHF with doxorubicin increases substantially at cumulative doses of 450–550 mg/m^2 and higher (Figure 1) [27] and with epirubicin at cumulative doses of 900–1000 mg/m^2 and higher [29, 30]. Each dose of anthracycline appears to result in the death of cardiac myocytes. The heart has well-developed compensatory mechanisms, but when these are overwhelmed, chronic dilated cardiomyopathy develops [31]. Importantly, there is considerable variation between patients in their susceptibility to cardiotoxicity and in their compensatory mechanisms [27].

It is difficult to estimate the true incidence of anthracycline-induced cardiotoxicity because studies have varied in their definitions, the methods used for measurement of heart function, and the underlying risk of the patient population [31]. Data are also primarily retrospective and long-term data are often not available [25]. Early retrospective data indicate that the incidence of CHF is ~3.0% in patients receiving a cumulative doxorubicin dose of 400 mg/m^2 increasing to 7.5% at 550 mg/m^2 and to 18.0% at 700 mg/m^2 [27]. The incidence was found to be lower with a once-weekly schedule compared with a 3-weekly schedule of doxorubicin administration, suggesting that peak concentrations maybe important in myocardial toxicity [27]. A higher incidence of CHF was reported in a retrospective analysis of three prospective studies, two of which were conducted in patients with breast cancer. The estimated cumulative percentage of patients with doxorubicin-related CHF was 5.0% at a cumulative dose of 400 mg/m^2, 26.0% at 550 mg/m^2, and 48.0% at 700 mg/m^2 [2].

For epirubicin, a large retrospective study reported that the cumulative risk of cardiotoxicity increased from 1.9% at doses of 800 mg/m^2 to 4.3% at doses of 900 mg/m^2 and 15.0% at 1000 mg/m^2 [29]. In another study of 105 patients with metastatic breast cancer referred for epirubicin/paclitaxel (Taxol: Bristol-Myers Squibb Pharmaceuticals Ltd, UK) treatment, the cumulative risk of developing CHF was estimated at 7.7% at a cumulative dose of epirubicin of 720 mg/m^2 and 48.7% at a cumulative dose of 1080 mg/m^2 [32].

Subclinical, late cardiomyopathy may occur in patients treated with doxorubicin in the absence of CHF, even in patients who received a cumulative dose of doxorubicin <550 mg/m^2. In a retrospective study of 141 patients with lymphoma, doxorubicin-induced left ventricular dysfunction with decreased fractional shortening (FS; <25%—a measure of myocardial contractility) was found in 39 of 141 patients (27.6%), most of whom had previously received a total dose of doxorubicin <300 mg/m^2 [33]. A further study, in which the cumulative dose of doxorubicin was 240 mg/m^2, found that adjuvant doxorubicin plus cyclophosphamide chemotherapy

Table 2. Cardiotoxicity in relation to cumulative dose

Study	Malignancy	Therapy	Cumulative dose, mg/m^2	CHF (%)[a]
Von Hoff et al. [27]	Various	Doxorubicin	400	3.0[b]
			550	7.5[b]
Swain et al. [2]	Breast cancer	Doxorubicin	400	5.0[c]
			550	26.0[c]
	Lung cancer		700	48.0[c]
Ryberg et al. [29]	Metastatic breast cancer	Epirubicin	800	1.9[b]
			900	4.0[b]
			1000	15.0[b]
Gennari et al. [32]	Metastatic breast cancer	Epirubicin/ paclitaxel	720	7.7[b]
			1080	48.7[b]

[a]Study definitions of chronic heart failure (CHF)—Von Hoff et al. [27]: a case of doxorubicin-induced CHF was defined as the clinical signs and symptoms of CHF believed to be secondary to doxorubicin by the clinical investigator caring for the patient; Swain et al. [2]: the protocol definition of CHF included two or more of the following—cardiomegaly on chest X-ray; basilar rales; S_3 gallop; or paroxysmal nocturnal dyspnea, orthopnea, or significant dyspnea on exertion; Ryberg et al. [29]: patients registered as having CHF should fulfil the following criteria—(i) a history of breathlessness, (ii) clinical signs of CHF (dyspnea/congestion on chest X-ray or peripheral edema, (iii) X-ray showing cardiomegaly with or without pulmonary congestion/pleural effusion, and/or (iv) abnormal left ventricular ejection fraction (LVEF) (LVEF < 46% absolute value or a decrease in LVEF ≥ 15%) and if possible also an abnormal echocardiography; Gennari et al. [32]: the diagnostic criteria for CHF were new onset of dyspnea, presence of peripheral edema, cardiac enlargement or pulmonary congestion on chest radiograph, or pulmonary rales at auscultation. When a patient had clinical symptoms of CHF, reduced LVEF contributed to the diagnosis, and its assessment was carried out by bidimensional echocardiography.

[b]Cumulative risk of developing CHF.

[c]Estimated cumulative percentage of patients with doxorubicin-related CHF.

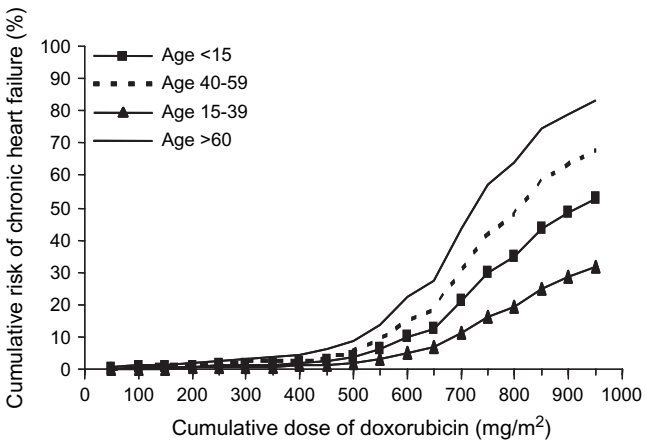

Figure 1. Cumulative probability of developing doxorubicin-induced chronic heart failure [27]. Cumulative probability of developing doxorubicin-induced chronic heart failure versus total cumulative dose of doxorubicin for patients in four arbitrary age categories following drug administration on an once every 3-week schedule.

was associated with frequent, acute decreases in LVEF when measured 3 weeks after the fourth cycle of treatment [34]. In this study of 1572 eligible women with early-stage breast cancer who completed treatment, 1458 had pre- and postadjuvant doxorubicin plus cyclophosphamide LVEF measurements. Among these women, over half (51.1%) had at least a 15% decrease in LVEF, but this remained at or above the radiological lower limit of normal [34]. Similarly, recent data show that subtle cardiac abnormalities may occur at epirubicin doses significantly below those known to be potentially clinically harmful [3, 35]. In a phase II, open, nonrandomised trial of 16 epirubicin-treated patients with cancer, it was reported that measurable systolic dysfunction may appear at a dose level of 200 mg/m^2 of epirubicin [3].

These data highlight the importance of new methods of early identification of patients at risk for CHF at the lowest doses of anthracyclines, to optimise the use of chemotherapy and reduce cardiac damage [3]. Further, based on the above data, previous anthracycline exposure should be considered a cardiovascular risk factor when considering treatment options in the metastatic setting.

dosing schedules. Clinical studies have shown that the incidence of acute and chronic cardiotoxicity may depend on the rate of anthracycline administration during each session and on the schedule of delivery. Early studies have reported that continuous infusions of free doxorubicin between 48 and 96 h reduced cardiotoxicity [36, 37]. Furthermore, the therapeutic efficacy of doxorubicin was not compromised by continuous infusion [36]. A more recent meta-analysis of five randomised controlled trials in which different anthracycline dosage schedules were compared in cancer patients showed a statistically significant lower rate of CHF with an anthracycline infusion duration of 6 h or longer as compared with a shorter infusion duration ($P = 0.01$). An infusion duration of 6 h or longer also appeared to reduce the risk of subclinical cardiac damage [38].

Retrospective analyses have found that weekly doses of doxorubicin are considerably less cardiotoxic than administering the drug every 3 weeks. Multivariate analysis of risk factors for doxorubicin cardiotoxicity showed that doxorubicin therapy administered on a weekly schedule is associated with less anthracycline-induced cardiac damage than when it is delivered in the conventional, 3-weekly schedule ($P = 0.002$) [39]. These findings are supported by an earlier retrospective study in which three major types of drug schedule were used: single doses repeated every 3 weeks, three consecutive daily doses repeated every 3 weeks, and weekly doses [27]. The corresponding overall incidences of drug-induced CHF were 2.9%, 2.4%, and 0.8%, respectively [27].

effect of other interventions and treatments

A number of other therapies may also have adverse cardiac effects in women with advanced breast cancer, which could contribute to the overall cardiac risk for these patients or potentially exacerbate anthracycline-associated cardiotoxicity.

radiation therapy. Radiation therapy to the thorax may induce both early and late cardiac effects if parts of the heart have been included in the irradiation field [40]. Studies have shown that anthracycline-associated cardiac damage may become clinically more evident in patients who have already received cardiac injury from radiotherapy [32, 41–43]. In a study of 105 patients with metastatic breast cancer, the cumulative risk of developing CHF after an epirubicin/paclitaxel-containing regimen was low up to cumulative epirubicin doses of 990 mg/m^2; however, the risk of developing cardiac failure increased dramatically when a cumulative dose >990 mg/m^2 was reached, particularly in patients with another cardiovascular risk factor, such as previous radiotherapy to the chest wall [32]. However, modern methods of breast/chest wall radiation, such as intensity-modulated radiation therapy, now avoid any appreciable dose to the heart in most patients.

co-administration of additional agents. A number of studies have reported a synergistic effect on cardiotoxicity when anthracyclines are administered with other agents. However, a significant issue when interpreting the results of these studies is that cardiotoxicity is not defined consistently.

It is well documented that anthracyclines and trastuzumab have synergistic effects on cardiac dysfunction when administered concomitantly [44, 45]. In a phase III trial by Slamon et al. [44], New York Heart Association (NYHA) III/IV heart failure was observed in 16% of patients treated with trastuzumab concurrently with anthracycline and cyclophosphamide, compared with 3% in those treated with anthracycline and cyclophosphamide. A similar trend was reported from a study which showed that the incidence of CHF (NYHA III/IV) or death from cardiac causes was greater in patients who received concurrent treatment with doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab (4.1%) than in patients who did not receive trastuzumab as part of their treatment regimen (0.8%) [45].

Combinations of anthracyclines and paclitaxel have also been reported to result in a higher incidence of cardiotoxicity, although this is not a consistent finding in clinical trials [32, 46–49]. For instance, a randomised study of patients with metastatic breast cancer reported a greater incidence of CHF (NYHA II/III/IV) in patients treated concurrently with doxorubicin and paclitaxel than in patients treated with doxorubicin and cyclophosphamide, although the result was not statistically significant (3% versus 1%, respectively; $P = 0.62$) [49]. At a cumulative doxorubicin dose of 180 mg/m^2, patients treated with paclitaxel had a greater risk of cardiotoxicity than patients who did not receive paclitaxel [hazard ratio (HR) 2.5; $P = 0.002$] [49]. By contrast, in a retrospective analysis of 657 women with advanced breast cancer, combination therapy with doxorubicin and paclitaxel was associated with a cardiac risk similar to that of anthracycline monotherapy up to a cumulative anthracycline dose of 340–380 mg/m^2 [46]. Further research is therefore required to determine whether the addition of paclitaxel to an anthracycline regimen does in fact increase the risk of cardiotoxicity. However, the paclitaxel/doxorubicin studies do show a strong sequence dependency for this risk. This may be due to the carrier cremophor EL used in the formulation of the paclitaxel [50]. Giving paclitaxel before doxorubicin

produces higher plasma levels of the anthracycline as compared with the opposite sequence, which has therefore become the standard practice [51].

patient-related risk factors

age. Ageing remains one of the single greatest risk factors for breast cancer, with approximately 50% of all new breast cancers occurring in women aged 61 years or older [12]. Advanced age also appears to be a risk factor for the development of anthracycline-induced cardiomyopathy [2, 27, 33]. In an early retrospective analysis of the records of 4018 patients with cancer (mean age, 49 years) who had received doxorubicin, a steady increase in the risk of developing anthracycline-induced CHF was observed with increasing age ($P = 0.0002$ when comparing all age groups; Figure 1) [27]. These findings have been confirmed by more recent retrospective data that show age to be an important risk factor for doxorubicin-related CHF following a cumulative dose of 400 mg/m^2, with older patients (age > 65 years) being 2.25 times more likely to experience CHF compared with younger patients (age ≤ 65 years) [2].

An increase in cardiotoxic susceptibility with advancing age following treatment with epirubicin was demonstrated in a prospective study of 120 patients with advanced breast cancer [24]. Patients aged >50 years treated with a high cumulative dose of epirubicin (1000 mg/m^2) had a 68% actuarial risk of developing a severe (>25% decline in LVEF from baseline) reduction in cardiac function compared with 36% for patients <50 years of age ($P < 0.001$). In patients >50 years of age, the majority (68%) of cardiac events occurred in the postanthracycline period, with a median onset of 3–4 months [24].

preexisting cardiovascular disease or cardiac risk factors. At diagnosis, a substantial number of women with breast cancer are at significant risk of developing cardiovascular disease due to age and other major cardiac risk factors such as hypertension, diabetes, and obesity, which can adversely affect survival [4, 52]. The presence of a cardiac risk factor may increase the chance of a patient experiencing a treatment-related cardiac event, as suggested by an early retrospective study [27]. The probability of developing doxorubicin-induced CHF was higher in patients with previous cardiac disease or hypertension or both, although this was not statistically significant [27].

Weight ≥70 kg has also been identified as a predictive factor for cardiotoxicity in patients with metastatic breast cancer receiving doxorubicin ($P = 0.005$) [53]. An elevated body mass index (BMI) >27 kg/m^2 has been found to significantly correlate with the occurrence of left ventricular dysfunction after adjuvant epirubicin-based chemotherapy in early breast cancer patients [19]. In this study, left ventricular dysfunction occurred in 0.9% of the patient population with a BMI <27 kg/m^2 compared with 1.8% of patients with a BMI ≥27 kg/m^2. As well as having a generally evaluated risk for cardiovascular disease, overweight or obese patients receive proportionally larger doses of anthracyclines compared with average weight patients (when calculated on an mg/m^2 basis), which might result in increased acute cardiac dysfunction.

Not all published data, however, report a positive correlation between cardiac risk factors and increased cardiotoxicity. In a study of 105 patients with advanced breast cancer who received an epirubicin/paclitaxel-containing regimen, the cumulative probability of developing CHF was found to be similar in patients with and without at least one preexisting cardiovascular risk factor up to cumulative epirubicin doses of 990 mg/m^2 (cumulative risk, 10% and 12%, respectively) [32].

female sex. Female sex is an independent risk factor for cardiac abnormalities after treatment with doxorubicin for childhood cancer [54]. However, early studies of doxorubicin-induced cardiotoxicity in adult patients with various cancers, including breast, reported that gender did not influence the extent of the endomyocardial injury [39, 41]. Furthermore, in a study of 141 adult patients who had previously received doxorubicin-based chemotherapy for lymphoma, multivariate analysis showed a significant correlation between male sex and left ventricular dysfunction [33]. Controversy therefore remains as to whether female sex predisposes the patient to a greater risk of cardiotoxicity.

strategies to reduce the cardiotoxicity of anthracyclines

Several strategies are employed to reduce the incidence of anthracycline-associated cardiovascular complications. These include screening for both patient-related and treatment-related cardiac risk factors, modifying the schedule of anthracycline administration, careful monitoring for cardiac abnormalities, adopting an alternative strategy such as liposomal formulation, and opting for a chemotherapy regimen which does not incorporate an anthracycline.

screening for risk factors and prevention of cardiac events

It is recommended that patients should be assessed for preexisting cardiac risk factors before starting therapy with anthracyclines (Table 3). By analogy with other cardiac insults, the use of angiotensin-converting enzyme (ACE) inhibitors and/or beta blockers early in the course of the disease shows increased efficacy in the prevention of adverse cardiac events. There is evidence that pretreatment can abolish the fall in ejection fraction seen with high-dose chemotherapy [55, 56]. The long-term efficacy and tolerability of this strategy deserves to be tested in a clinical trial. However, it should be remembered that ACE inhibitors and beta blockers are not preventing myocyte apoptosis, the underlying mechanism of anthracycline toxicity; they are simply improving the heart's compensatory mechanisms [57], and thus, should not be regarded as an antidote, allowing higher doses of anthracycline to be given. If appropriate, patients should also be advised of ways to reduce their cardiac risk through stopping smoking, lipid and blood pressure lowering, increased exercise, and losing weight [4].

Table 3. Risk factors for anthracycline-induced cardiotoxicity

Treatment related
Cumulative dose of anthracycline
Dosing schedules
Previous anthracycline therapy
Radiation therapy
Co-administration of additional potentially cardiotoxic agents
Patient related
Age
Preexisting cardiovascular disease or cardiac risk factors (hypertension, diabetes, increasing total cholesterol)
Obesity
Smoking

dose limitation and schedule modification

The risk of anthracycline cardiotoxicity can be minimised by keeping the total lifetime cumulative dose of doxorubicin below the recommended threshold. It is generally recommended that the lifetime dose be <550 mg/m^2 for doxorubicin and 900 mg/m^2 for epirubicin. However, this approach will result in discontinuation of anthracycline administration to some patients who might gain further benefit from therapy [32].

Besides cumulative dose of anthracyclines, it has also been proposed that exposure to peak levels of anthracyclines maybe an important factor in the pathogenesis of anthracycline cardiotoxicity [58]. Since converting bolus injections of anthracycline into prolonged infusions has been reported to be less cardiotoxic [38], it has been proposed that a potential strategy to decrease the risk of anthracycline-induced cardiotoxicity is infusion over several hours [28]. Replacing bolus administration of anthracycline with slow infusion, however, remains controversial. Current good practice is to give a bolus via a fast-flowing saline infusion due to the increased risk of extravasation/tissue necrosis with vesicants. For infusing anthracyclines >24 h, there is the potential to use small infusion devices via a central line. This would reduce the risk of extravasation, but would potentially increase the risk of infections, costs of chemotherapy, and nursing time to set up and flush the line weekly. Additional costs of the procedure and chest X-rays to check line position would also need to be considered. In addition, some lines do not 'bleed back'; therefore, this would be a great concern when checking the position of the line before anthracycline administration. Overall, therefore, in the majority of cases, prolonged infusions are not recommended as a strategy to reduce anthracycline associated cardiotoxicity.

monitoring of anthracycline-induced cardiotoxicity

Active monitoring of patients' cardiac function can help guide the optimal delivery of chemotherapy, to minimise cumulative cardiotoxicity, while maintaining antitumour efficacy. A number of techniques are available, including the use of biopsy, imaging modalities, and, more recently, the development of specific markers of cardiac injury (Table 4).

endomyocardial biopsy. Endomyocardial biopsy has traditionally been viewed as the most reliable method for the evaluation of anthracycline cardiotoxicity [58]. Although this technique provides histological evidence of cardiotoxicity, it is not routinely carried out in clinical practice for obvious reasons [21]. Endomyocardial biopsy samples only a very small area of the right ventricular endocardium and does not provide data on myocardial function or the clinical state of the patient [58]. Its use is also limited by its invasive nature and the specialist input required for performing the procedure and interpreting the findings [59].

imaging techniques. Evaluation of LVEF has been adopted widely as the preferred option of assessing anthracycline cardiotoxicity [58]. However, there is currently no clear consensus on what degree of fall in LVEF represents a significant drop in myocardial contractile function. Several studies have recorded a drop in LVEF of >10 points or a fall below the institutional lower limit of normal as indicative of anthracycline-associated cardiotoxicity [11, 60–62]. However, such a drop is a late event in anthracycline-induced cardiotoxicity and, therefore, is not detectable until significant damage is already present [18].

Radionuclide ventriculography (multiple uptake gated acquisition scan) is an established, well-validated, and widely used method to determine ejection fraction [63]. Results from a recent retrospective analysis suggest that an incipient fall in LVEF detected on serial equilibrium radionuclide ventriculography during doxorubicin therapy provides an appropriate and cost-effective approach for predicting and preventing impending CHF [64].

Echocardiography is a widely used noninvasive method of monitoring the cardiotoxicity of cancer therapy. In contrast to radionuclide ventriculography, echocardiography does not involve the use of ionising radiation and provides a wider spectrum of information on cardiac morphology and function [63]. Parameters of systolic (LVEF, left ventricular FS, and systolic wall thickening) and diastolic function [mitral inflow pattern early/atrial (E/A) ratio, isovolumetric relaxation time, and pulmonary venous flow pattern] and valvular function can be assessed [63]. With modern echocardiography equipment and techniques, it is possible to obtain images in the vast majority of patients, although technical factors, such as the presence of a left-sided breast implant, can occasionally affect this [65].

advanced echocardiographic methods

two-dimensional echocardiography with Doppler. Tissue Doppler imaging allows the measurement of the diastolic and systolic velocities of the ventricular walls and mitral annulus [66]. In the evaluation of left ventricular diastolic performance, tissue Doppler imaging is more reliable than conventional Doppler because loading conditions influences it less [3].

In a recent prospective study, combined tissue Doppler imaging and two-dimensional echocardiography were used to

Table 4. Different methods of monitoring anthracycline-associated cardiotoxicity

Method	Benefits	Limitations
Endomyocardial biopsy	Provides histological evidence of cardiotoxicity	Invasive Requires specialist input for performing the procedure and interpreting the findings Small sample of myocardium tested
Radionuclide ventriculography (multiple uptake gated acquisition scan)	Well-established and well-validated method to determine ejection fraction Can also assess regional wall motion and diastolic function (nonstandard)	Invasive—exposes patients to radiation which limits its repeatability Low spatial resolution No information on valve function LVEF measurements are not sensitive for the early detection of preclinical cardiac disease
Echocardiography	Provides a wide spectrum of information on cardiac morphology and function Does not expose patients to ionising radiation Tissue Doppler imaging may improve detection of systolic and diastolic dysfunction	Image quality limits use in some patients LVEF measurements time consuming and operator dependent with limited reproducibility LVEF measurements are not sensitive for the early detection of preclinical cardiac disease Both FS and LVEF are affected by preload and afterload
Stress echocardiography	Cardiac abnormalities that remain occult at rest can be detected	Not routinely carried out Mixed reports on ability to enhance diagnostic sensitivity
Biomarkers	Troponin is a highly specific and sensitive biomarker for detection of myocardial damage Potentially useful screening tool	Data regarding clinical value are limited
Magnetic resonance imaging	Valuable tool to assess myocardial function and damage	High costs of repeated examinations Limited availability
Computed tomography	Image quality similar to magnetic resonance imaging Low temporal resolution	High radiation dose Limited availability
Scintigraphy	Sensitive method to detect myocyte damage in patients after doxorubicin therapy	Larger prospective trials required to ascertain potential role

LVEF, left ventricular ejection fraction; FS, fractional shortening.

evaluate the early and late effects of anthracycline chemotherapy in 20 adult patients who had no history of heart disease or exposure to chemotherapy and who required anthracycline therapy for breast cancer, lymphoma, or acute leukaemia [66]. Significant changes in left ventricular function were observed within a few months of the completion of chemotherapy, while changes in systolic function occurred later, together with even more pronounced changes. These changes were more pronounced for most tissue Doppler imaging measurements when compared with standard Doppler or ejection fraction evaluation [66]. Tissue Doppler imaging appears to offer significant advantages over traditional techniques, such as E/A ratio or deceleration time, when trying to determine the presence of isolated diastolic dysfunction as a result of anthracycline therapy [67]. Findings from a recent phase II, open, nonrandomised trial in a group of epirubicin-treated patients with cancer at different sites suggest that the combination of both tissue Doppler imaging parameters together with inflammatory/oxidative stress markers provides an earlier and more accurate evaluation of cardiac function changes during anthracycline therapy [3]. Although Doppler myocardial imaging data acquisition adds very little time to the conventional echocardiographic study, this has to be balanced with the increased time required to analyse the data [63].

Recently, the Tei-index, a Doppler echocardiographic parameter of global ventricular function, has been introduced to study the impact of anthracyclines on ventricular function [68]. In a prospective study of 100 adults who received anthracycline-based chemotherapy for cancer, the Tei-index was shown to increase in 78.8% of patients after anthracycline therapy compared with pretherapy values, indicating alteration of myocardial function [68]. Longer term follow-up is needed to determine whether the Tei-index can predict overall cardiac risk in patients receiving anthracycline-containing chemotherapy regimens [69, 70].

stress testing. In dobutamine stress echocardiography, escalating doses of dobutamine are infused in order to study the inotropic response (contractile reserve) of the myocardium; cardiac abnormalities that remain occult at rest can be detected [63]. Stress testing and dobutamine stress echocardiography have been studied extensively, with no consistent evidence that

it enhances diagnostic sensitivity in the survivor population [21, 71].

alternative monitoring methods

hormones and markers of cardiac damage. Cardiac troponins (I and T) are sensitive and specific markers of myocardial damage in myocardial infarction and myocarditis [72]. During anthracycline treatment, troponins can be released [72], and serum levels of cardiac troponin-T (cTnT) are recognised as biochemical markers of myocardial injury [73]. cTnT, a component of the troponin complex of cardiac muscle cells, is elevated in some patients who have received anthracyclines and it is associated with dysfunction of the left ventricle [74]. Based on clinical trial data, it has been suggested that the measurement of the cTnT could be useful for the detection of anthracycline cardiotoxicity in the early stages. However, this study is limited by the low number of patients studied, their short mean follow-up (<1 year), and the lower cumulative anthracycline doses than those recognised to be cardiotoxic [74].

Clinically apparent cardiac injury can also be determined by natriuretic peptides, which are released from the atria (atrial natriuretic peptide) and the left ventricle [brain natriuretic peptide (BNP)] in response to circulating volume and intracardiac pressures [25]. Findings from a recent study, which prospectively assessed 100 adults who received anthracycline-based chemotherapy over a period of 1 year, suggest that, at present, the measurements of cTnT or BNP should not safely replace serial echocardiographic evaluation of systolic and diastolic function for the monitoring of anthracycline cardiotoxicity [68]. Based on current data, however, it has been proposed that biomarker monitoring of patients during anthracycline exposure may provide crucial evidence of early damage that has not previously been appreciated [75]. As data regarding these biomarkers are still limited, they are not measured routinely [63].

magnetic resonance imaging. Magnetic resonance imaging (MRI) is an alternative method used for assessment of myocardial function, perfusion, and tissue characterisation [63]. MRI systolic function assessment is based on both the visual analysis of wall motion and volumetric measurements. In general, the spatial resolution of MRI is comparable to echocardiography; however, temporal resolution is significantly lower [63]. Although MRI maybe considered a valuable tool to assess myocardial function and damage, additional, larger studies will be needed to confirm these findings and to further test the prognostic value of contrast-enhanced MRI. Furthermore, due to the high costs of repeated examinations and limited availability, MRI is not an ideal first-line screening test at present, but may have potential in the future [63].

computed tomography. The image quality with cardiac computed tomography is similar to MRI, but its temporal resolution is more limited [63]. To date, no data are available in the clinical setting of chemotherapy patients, and due to the high radiation dose and its limited availability, it is not considered a feasible tool to assess cardiac function [63].

scintigraphy. To date, various scintigraphic strategies have been evaluated for the early detection of anthracycline-induced cardiac damage [40]. Indium-111-antimyosin scintigraphy has been investigated as a noninvasive means of assessing anthracycline-induced cardiotoxicity in breast cancer patients [76, 77]. Data indicate that antimyosin studies are a sensitive method of detecting myocyte damage in patients after doxorubicin therapy [77]. However, larger prospective trials are required to ascertain the potential role of these imaging modalities [63].

It is recommended that all patients undergo a baseline assessment of cardiac function before commencing anthracycline therapy. Ideally, the chosen method should be highly sensitive, specific, and noninvasive [78] and one with which the centre is familiar. In addition, the specificity of any test should allow for an accurate risk-benefit analysis in balancing the possibility of cardiac dysfunction with greater drug doses, against the potential harm resulting from withholding antitumour therapy [79]. For patients with a better prognosis, it might also be appropriate to monitor cardiac function at a point during treatment and/or after the final cycle of treatment to detect any early, preclinical signs of dysfunction.

alternative anthracycline strategies

liposomal anthracyclines. Liposomal anthracycline formulations have been developed to increase the therapeutic index of free anthracyclines. The encapsulation of a cytostatic agent within a macromolecular vector, such as a liposome, significantly reduces its distribution volume, diminishing its diffusion and consequently, the toxicity for healthy tissues while increasing the concentration within the neoplastic tissue [80]. There are two formulations of liposomal anthracyclines: nonpegylated and pegylated. Several clinical trials have examined the effectiveness of these formulations of doxorubicin and have shown them to have similar efficacy with less cardiac toxicity when compared with free doxorubicin [11, 60, 61].

In a phase III trial of 509 women with metastatic breast cancer, pegylated liposomal doxorubicin 50 mg/m^2 (every 4 weeks) provided comparable efficacy (median progression-free survival 6.9 versus 7.8 months; HR 1.00) to free doxorubicin 60 mg/m^2 (every 3 weeks), with significantly reduced cardiotoxicity (4% versus 19%; HR 3.16; $P < 0.001$) [60]. There was less risk of developing cardiotoxicity with pegylated liposomal doxorubicin than with doxorubicin in all subgroups analysed, including those subgroups at increased cardiac risk (≥65 years of age, prior adjuvant anthracycline, cardiac risk factors) [60]. Pegylated liposomal doxorubicin, however, may accumulate in the skin and is associated with palmar–plantar erythrodysesthesia (PPE; hand–foot syndrome) [81].

Two randomised phase III trials have shown that nonpegylated liposomal doxorubicin was significantly less cardiotoxic than conventional doxorubicin in the first-line treatment of metastatic breast cancer (13% versus 29% patients, $P = 0.0001$ [11]; 6% versus 21% patients, $P = 0.0001$ [61]), while providing comparable antitumour activity (response rate 26% in both groups [11]; 43% in both groups [61]). In addition, there was a trend towards less toxicity in the nonpegylated liposomal doxorubicin group, with less grade 3 or 4 diarrhoea and nausea/vomiting and less grade 4 neutropaenia [17]. PPE was a rare side-effect of nonpegylated liposomal

doxorubicin, occurring in <0.5% of patients in the two phase III studies [11, 61].

The results from a retrospective analysis, based on data from the two randomised phase III trials [11, 61], suggest that patients with breast cancer who relapse later than 6 months after anthracycline treatment in the adjuvant setting may respond to anthracycline-based treatment of metastatic disease [82]. In addition, there may be greater benefit from nonpegylated liposomal doxorubicin than free doxorubicin in the first-line treatment of these patients, as demonstrated by a significantly higher overall response rate (31% versus 11%, $P = 0.04$) and a significantly prolonged time to treatment failure (median 4.2 versus 2.1 months, $P = 0.01$) [82]. Findings from a meta-analysis that compared non-pegylated liposomal doxorubicin with free doxorubicin also showed a statistically significant lower rate of clinical [relative risk (RR) 0.20, 95% confidence interval (CI) 0.05–0.75; $P = 0.02$] and clinical and subclinical (RR 0.38, 95% CI 0.24–0.59; $P = 0.00001$) heart failure with nonpegylated liposomal doxorubicin [17].

In a comparative trial of 160 anthracycline-naive metastatic breast cancer patients, both nonpegylated liposomal doxorubicin and epirubicin had relatively low rates of cardiotoxicity at a maximum cumulative dose of 600 mg/m^2 (11.8% versus 10.3%, respectively) [62]. Nonpegylated liposomal doxorubicin was also superior to epirubicin with respect to median time to treatment failure (5.7 versus 4.4 months; $P = 0.007$) and median time to disease progression (7.7 versus 5.6 months; $P = 0.022$) [62].

Based on the above data, liposomal doxorubicin should be considered as a treatment option for patients with metastatic breast cancer who are at cardiac risk. Furthermore, nonpegylated liposomal doxorubicin may have efficacy as well as cardiotoxicity advantages over free doxorubicin for patients treated adjuvantly with anthracyclines.

iron-chelating agents. Dexrazoxane is an iron-chelating agent that is thought to decrease the cardiotoxic effect of doxorubicin by blocking the generation of free radicals. Although its benefits against delayed cardiomyopathy remain unknown, it is known to decrease the immediate cardiotoxicity of doxorubicin [28]. In a recent meta-analysis of six randomised controlled trials, the majority of which enrolled adults with advanced breast cancer, dexrazoxane was found to prevent heart damage; however, it was suggested that patients treated with it might have a lower antitumour response rate to the anthracycline treatment [83]. Hence, although dexrazoxane maybe considered as a potential strategy to reduce anthracycline cardiotoxicity; its use should be weighed against the possible risk of a lower response rate and the additional costs of treatment.

chemotherapy regimens which do not include an anthracycline

One strategy to reduce anthracycline-associated cardiotoxicity is simply not to use an anthracycline. Although taxanes as a class of chemotherapeutic agent are known to carry a potential cardiovascular risk [4], a study comparing doxorubicin plus cyclophosphamide with docetaxel (Taxotere: Sanofi-Aventis, UK) plus cyclophosphamide has shown that treatment with docetaxel conferred no apparent cardiotoxicity [84]. However, while a recent meta-analysis has shown taxanes to be equivalent to single-agent anthracyclines in terms of response rates and survival, taxanes were significantly less effective than anthracyclines in terms of progression-free survival [85]. Thus, the choice of a less cardiotoxic agent *per se* than an anthracycline should be balanced against a potential reduction in efficacy and against the overall toxicity profile of the two agents.

treatment of cardiac events

Cardiotoxicity which occurs during anthracycline treatment or in the first year after its completion is often manifesting as arrhythmias, such as atrial fibrillation or pericarditis. These should be fully assessed and treated according to standard guidelines, which may include the use of heart rate or rhythm-modifying drugs and antithrombotic agents [15]. Patients with symptomatic CHF should receive ACE inhibitors and beta blockers with diuretics when fluid over-load is present [86]. It is recommended that clinicians follow the guidelines set out by the National Institute for Health and Clinical Excellence for the management of CHF [87], with early review by cardiology services.

conclusions

Strategies to prevent and manage anthracycline-induced cardiotoxicity are important for all advanced breast cancer patients. Ideally, these should be initiated before anthracycline therapy, in order to minimise the possibility of irreversible cardiac damage. In addition to screening patients for patient- and treatment-related cardiovascular risk factors, proactive treatment of modifiable risk factors should also be undertaken (e.g. hypertensive patients should receive medication such as ACE inhibitors and other life-style advice to reduce blood pressure before and during anthracycline treatment). Cardiac function should also be accurately assessed before starting anthracycline therapy; for high-risk patients with a good prognosis, repeat assessments during and after treatment should also be considered. Furthermore, the chosen method of assessment should be one with which the centre is familiar. Lifetime cumulative anthracycline dose should be limited to within recommended limits (450–550 and 800–1000 mg/m^2 for doxorubicin and epirubicin, respectively), and consideration should also be given to using a less cardiotoxic regimen, such as employing an alternative to anthracycline treatment or using a liposomal preparation. Taking into account cost and other practical considerations, the latter strategy would be of particular benefit to patients who have previously received anthracyclines in the adjuvant setting or who are known to have reduced cardiac function, as nonpegylated liposomal doxorubicin appears to have efficacy and cardiotoxicity advantages over free doxorubicin in these patients.

Our key recommendations:

(i) Vigilant screening for both patient-related and treatment-related cardiovascular risk factors.

(ii) Accurate monitoring of patient cardiac function, before, during, and after anthracycline treatment.
(iii) Limiting lifetime cumulative anthracycline dose.
(iv) Choosing an alternative to anthracycline treatment or using a liposomal preparation.

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