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REVIEW

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Pharmacological strategies to reduce anthracycline-associated cardiotoxicity in cancer patients

Anna Stansfeld [a], Utsav Radia[a], Caitriona Goggin[a], Preethika Mahalingam[a], Charlotte Benson[a], Andrea Napolitano[a], Robin L Jones[a], Stuart D Rosen[b] and Vasilios Karavasilis[c]

[a]Medical Oncology, The Royal Marsden Hospital NHS Foundation Trust and Institute of Cancer Research, UK; [b]Cardiology, London North West University Healthcare NHS Trust and Royal Brompton Hospitals, UK; [c]Medical Oncology, University College London Hospitals NHS Foundation Trust, UK

ABSTRACT

Introduction: Anthracycline chemotherapeutic agents are widely used in the treatment of hematological and solid tumors, working principally through DNA intercalation and topoisomerase II inhibition. However, they are also well known to have cardiotoxic sequelae, commonly denoted as a reduction in ejection fraction. Drug-associated cardiotoxicity remains a significant limiting factor in the use of anthracyclines.

Areas covered: In this review, we explore the potential mechanisms of anthracycline-associated cardiotoxicity, identifying high-risk cohorts and approaches to cardiovascular monitoring. The mechanisms through which cardiotoxicity occurs are complex and diverse, ultimately leading to increased oxidative stress, mitochondrial dysfunction, and subsequent cellular apoptosis. Many of the cardiotoxic effects of anthracyclines exhibit a dose-dependent cumulative relationship and are more apparent in patients with previously existing cardiovascular risk factors. Long-term cardiovascular monitoring and optimization of risk factors, prior to commencing treatment as well as beyond the time of treatment, is therefore essential.

Expert opinion: We discuss some of the pharmacological strategies proposed to mitigate anthracycline-associated cardiotoxicity as well as prevention strategies to reduce the burden of coexisting cardiovascular risk factors. We highlight methods of early detection of patient cohorts who are at increased risk of developing anthracycline-associated cardiotoxicity and identify potential avenues for further research.

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1. Introduction

Anthracyclines are a widely utilized group of chemotherapeutic agents used across a broad range of different solid and hematological malignancies. This class of drugs includes commonly used agents: doxorubicin, epirubicin, daunorubicin, and actinomycin. The mechanism of action of anthracyclines involves DNA intercalation and subsequent topoisomerase II inhibition. Anthracycline administration leads to the production of free radicals, which have associated antitumor effects [1]. The way in which free radicals also contribute to myocardial damage will be later explored.

The relationship between anthracycline dosing and cardiotoxicity was well described in the 1970s, as Von Hoff et al. described the increasing risk of congestive cardiac failure associated with increased cumulative dosing of anthracycline. In 1977, Von Hoff described the pattern of congestive cardiac failure related to dosing of daunorubicin in 5,613 adult and pediatric patients and identified the important phenomenon of a dose-dependent relationship between the drug and cardiotoxicity [2]. In exploring this further, Von Hoff et al. described the increased incidence related to cumulative dosing and reported the likelihood of developing clinical cardiac failure related to doxorubicin use as 3% at 400 mg/m^2 total cumulative dose, 7% at 550 mg/m^2, and 18% at 700 mg/m^2 [3] (Figure 1). Similarly, in 1978, Friedman et al. report an increased incidence of cardiomyopathy when doxorubicin dosing exceeds 550 mg/m^2 total cumulative dose [4]. In more recent work, the incidence of cardiotoxicity is reported as even higher, with Swain et al. describing an incidence of 26% of doxorubicin-related congestive cardiac failure with cumulative doses above 550 mg/m^2 [5]. This higher incidence may relate to an earlier under-detection of anthracycline-associated cardiotoxicity and reflect the introduction of more sensitive monitoring tests now readily available. The frequency of cardiotoxicity in all patients treated with anthracycline is described as common [6]. Since the 1970s, prescribers have continued to use the above guidelines for anthracycline prescribing, taking care to not exceed the lifetime cumulative equivalent dose of doxorubicin of 550 mg/m^2.

This review will offer an overview of the proposed cellular etiology of anthracycline-associated cardiotoxicity, as well as recommendations for current cardiac monitoring before presenting an expert opinion on current pharmacotherapeutic

CONTACT Anna Stansfeld anna.stansfeld@nhs.net The Royal Marsden Hospital NHS Foundation Trust and Institute of Cancer Research

Article highlights

- Anthracycline chemotherapeutic agents are widely used in treating hematological and solid organ tumors; however, they have well-known dose-dependent cardiotoxic sequelae which limits their use in clinical practice.
- Anthracycline-associated cardiotoxicity occurs through various mechanisms, leading to increased oxidative stress, disruption of iron homeostasis and mitochondrial dysfunction which ultimately leads to cellular apoptosis.
- Anthracycline-associated cardiotoxicity was previously recognized by a reduction in ejection fraction. More recently, it is recognized as a combination of clinical symptoms as well as numerical parameters of myocardial function.
- Risk factor stratification of patients allows early identification of those who may be more susceptible to anthracycline-associated cardiotoxicity, and we recommend an early multi-disciplinary approach with specialist cardio-oncology review.
- The use of liposomal doxorubicin, or the addition of the cardioprotective agent dexrazoxane may ameliorate the risk to patients and reduce the incidence of anthracycline-associated cardiotoxicity. These pharmacological strategies may be used alongside primary and secondary prevention strategies for cardiac failure.

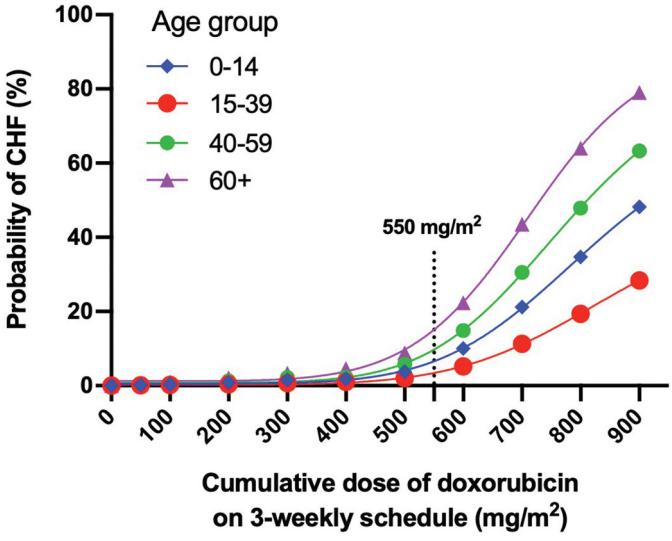

Figure 1. Relationship between cumulative doxorubicin dose and probability of developing congestive heart failure (CHF), stratified by age group. Adapted from data available in reference [3].

strategies available to reduce the risk to patients as well as suggestions for future research moving forward.

2. Mechanisms of anthracycline-associated cardiotoxicity

The effects of anthracyclines on cardiac myocytes are broadly described as two types: type 1 effects, which involve cell necrosis or apoptosis which is irreversible; and type 2 effects, which involve cell dysfunction and may be reversible [7]. A number of theories have been proposed, most of which revolve around anthracycline-mediated oxidative damage – both via reactive oxygen species (ROS) generation and mitochondrial toxicity. We will use the commonest anthracycline, doxorubicin, as our focus, as this is the mostly investigated agent, and also is predominantly used in the treatment of soft tissue and bone sarcomas.

2.1. Theory 1: increased reactive oxygen species (ROS)

Doxorubicin is metabolized *in vivo* via the mitochondrial respiratory chain, where it undergoes one- or two-electron reduction by oxidoreductases (i.e. NADH dehydrogenase, xanthine oxidase or nitric oxide synthase). The one-electron reduction by NADH dehydrogenase leads to formation of a doxorubicin-semiquinone radical which subsequently reacts with molecular oxygen to form the superoxide radical [8]. Further redox cycling of the superoxide radical leads to formation of the hydroxyl radical and hydrogen peroxide – both of which go on to cause oxidative cellular damage. As cardiomyocytes are highly reliant on oxidative substrate metabolism and have greater mitochondrial volume when compared with other body tissues, it is likely that this leads to selective damage from doxorubicin-mediated oxidant damage.

In vivo studies of transgenic mouse models treated with doxorubicin showed increasing expression of inducible Nitric Oxide Synthase (iNOS) and manganese superoxide dismutase (Mn-SOD), mitochondrial enzymes that reduce ROS burden, leads to reduced cardiomyocyte apoptosis and improved resting left ventricular function. Conversely, reducing iNOS expression led to a decrease in resting left ventricular function as well as blunted positive inotropic response to synthetic catecholamines [9]. Furthermore, deletion of nitric oxide synthase 3 (NOS3), involved in the metabolism of doxorubicin, in transgenic mice significantly reduced decline in left ventricular function following doxorubicin [10].

2.2. Theory 2: iron reducing substances

Doxorubicin also forms complexes with cellular iron, through proposed dysregulation of iron-regulatory proteins (IRPs), which leads to doxorubicin-iron complexes [11]. These doxorubicin-iron complexes catalyze a Fenton-like reaction whereby Fe^{2+} ions convert cellular hydrogen peroxide to hydroxyl and hydroperoxyl radicals – thus causing ongoing cellular damage and triggering apoptosis. This is extensively discussed in previous literature [12] as well as proposals for potential pharmacological targets [13].

2.3. Theory 3: mitochondrial disruption

Most of the aforementioned mechanisms of anthracycline toxicity lead to the common outcome of triggering cellular apoptosis. Doxorubicin treatment of cardiomyocytes has been shown to activate cellular caspases, increase mitochondrial permeability and release of mitochondrial enzymes into the cytosol, thus triggering cell apoptosis. Doxorubicin has also been demonstrated to bind to the mitochondrial phospholipid cardiolipin, thereby enhancing cytochrome C release [14]. This effect is reduced in cardiolipin-deficient cells [15]. Doxorubicin

can also trigger apoptosis via activation of phosphoinositide-3-kinases (PI3K), which inhibit the activity of cellular Akt. In vivo models have shown that over-expression of anti-apoptotic proteins such as Bcl-XL and Bcl-2 may offer a cardioprotective phenotype [16,17]. Increased Akt signaling through adenoviral vectors in murine myocardium treated with doxorubicin has shown improvement in LV function and reversal of doxorubicin-associated cardiac growth inhibition [18].

2.4. Theory 4: dysregulation of the renin-angiotensin-aldosterone-system (RAAS)

There have been a number of theories with inconclusive evidence with regard to RAAS. Doxorubicin alters gene expression through its activity and this may include elements of the RAAS. Doxorubicin may enhance signaling of Angiotensin-II receptors and cause increased synthesis of Angiotensin-II: though this is based only on cyclooxygenase-2 knockout murine models treated with Angiotensin-II receptor antagonists [19].

2.5. Theory 5: secondary alcohol metabolites

As discussed, the two-electron reduction by NADH dehydrogenase results in the formation of secondary alcohol metabolites, considered potentially causative in long-term anthracycline-associated cardiotoxicity [20]. The metabolites are commonly referred to as doxorubicinol (DOXOL), epirubicinol, daunorubicinol. This conversion occurs in the heart, and these metabolites accumulate and are not cleared as rapidly as anthracyclines. The resultant effect is that the increasing potency of the secondary alcohol metabolites cause greater cardiotoxicity than either the parent anthracycline drug, or the ROS. Proposed mechanisms for causing damage include the inactivation of calcium-channels and the interruption of iron homeostasis within a cell. The long-term accumulation of DOXOL, as opposed to doxorubicin, may indicate that the metabolite is the more toxic precipitant at a time beyond treatment completion when cardiotoxic events occur long after treatment is complete [21].

2.6. Theory 6: anthracycline-DNA-topoisomerase II complexes

The anti-cancer activity of doxorubicin relates to the formation of anthracycline-topoisomerase II-DNA complexes and subsequent topoisomerase II inhibition. Anthracyclines form a complex with topoisomerase II as well as DNA strands. Topoisomerase II is subsequently unable to break the stable anthracycline-DNA-topoisomerase II complex; this halts the DNA replication process and leads to exposed double-stranded breaks in DNA which subsequently trigger cellular apoptosis [1].

Topoisomerase IIα is present only in proliferating and tumor cells and is involved in DNA replication. The high levels of expression of topoisomerase IIα in cancer cells may correlate with the efficacy of anthracyclines as chemotherapeutic agents. Conversely, topoisomerase IIβ is present in all cells, and is involved in DNA transcription. Topoisomerase IIβ is expressed in cardiac tissue unlike topoisomerase IIα, and the specific complexes involving this isoenzyme may lead to cardiomyocyte necrosis and cell death [22].

As will later be discussed, the significance of the isoenzyme topoisomerase IIβ being implicated in the etiology of anthracycline-associated cardiotoxicity may help to explain the cardioprotective role of dexrazoxane.

3. Defining anthracycline-associated cardiotoxicity

A single consensus definition is lacking with regard to treatment-related cardiotoxicity. Curigliano et al. define cardiotoxicity as a reduction in left ventricular ejection fraction (LVEF) of at least 5% to less than 55% with accompanying signs or symptoms of cardiac failure, or a reduction in LVEF of at least 10% to below 55% in an asymptomatic patient [23]. This definition was originally developed by the Cardiac Review and Evaluation Committee supervising trastuzumab clinical trials [24].

More recently, the International Cardio-Oncology Society 2021 Consensus separates Cancer-therapeutics Related Cardiac Dysfunction (CTRCD) into symptomatic and asymptomatic groups. Assessing LVEF parameters, cardiac biomarkers, global longitudinal strain (GLS), and clinical symptoms allows further division into mild, moderate, severe, and very severe categories. These parameters are comparable to those used in the Common Terminology Criteria for Adverse Events (CTCAE), used in clinical trials – thus allowing the same definitions to be used in clinical practice and research [25].

The onset of anthracycline-associated cardiotoxicity can be stratified into acute, early-onset chronic progressive and late-onset chronic progressive. Acute onset refers to often reversible symptoms commencing immediately following, or within 14 days of anthracycline administration. Early-onset chronic progressive starts within 1 year of completion of treatment or during treatment. Late-onset chronic progressive occurs more than 1 year after treatment [23].

Early or late chronic progressive cardiotoxicity may present as dilated cardiomyopathy and not be clinically evident for many years following treatment. The chronic progressive nature of these two subtypes indicates a poor prognosis and historically was believed to be irreversible [26].

4. Risk factors

In discussing the role of preventing anthracycline-associated cardiotoxicity, it is important to recognize the potential long-term consequences of the use of these agents. Armstrong et al. identified the increased risk for cardiac events in childhood cancer survivors who had received anthracycline chemotherapy or other treatments such as chest-directed radiotherapy [27]. They demonstrated that the additional presence of cardiovascular risk factors significantly increased the subsequent risk further of coronary vascular disease, heart failure, and valvular heart disease. In the group who had received anthracycline chemotherapy, hypertension was identified as a significant risk factor for the development of heart failure, as well as hypertension when also combined with concurrent diagnoses of diabetes and dyslipidemia [27].

Lipshultz et al. describe the progressive and disabling effects of cardiotoxicity in childhood cancer survivors and highlight the importance of prioritizing the identification and prevention of long-term cardiovascular risk when treating a pediatric population [28]. Early intervention for modifiable risk factors such as obesity, inactivity, diabetes, and smoking helps to reduce the incidence of cardiovascular disease in survivors of childhood cancer. As well as addressing risk factors, close monitoring and early detection of cardiotoxicity is important [29].

The monitoring of patients who have received cardiotoxic anti-cancer treatments remains important far beyond the time of treatment completion. Optimizing the control of modifiable risk factors in years beyond treatment completion can play an important role in reducing future cardiac events.

In addition to lifestyle related modifiable risk factors as discussed, it is important to consider preexisting cancer-related risk factors. These may include prior treatment with cardiotoxic systemic therapy or radiotherapy, direct tumor invasion of the heart or vessels, and cancer mediated hypercoagulability [30].

Consideration should be given to genetic predisposition as a risk factor toward anthracycline-associated cardiotoxicity. Visscher et al. validated genetic variants in two genes (UGT1A6 and SLC28A3) which were predictive of the development of anthracycline-associated cardiotoxicity in a pediatric population. A prediction model developed which also accounted for clinical factors better predicted patients at risk of cardiotoxicity as compared to clinical factors alone [31]. The development of pharmacogenomic modeling enabled researchers to stratify patients into high- and low-risk groups taking into account both genetic variants identified and clinical factors [32]. Whilst the identification of patients at high risk is important to allow careful dosing, monitoring, and prevention strategies; it is also important to identify those patients at low risk of developing cardiotoxicity. This may highlight a population who can tolerate higher cumulative doses of anthracyclines, or who may indeed require fewer monitoring visits [33].

The optimization of cardiac function is important beyond the completion of cancer treatment, but also it is imperative to consider prior to starting anthracycline-based chemotherapy. As earlier discussed, preexisting hypertension is likely to lower the threshold of the development of anthracycline-associated cardiotoxicity in our patients [34].

It is important to consider the baseline cardiac function of a patient prior to commencing cardiotoxic treatment and to address cardiovascular risk factors accordingly. Early intervention, both lifestyle and pharmacological, should be encouraged with a multi-disciplinary approach between cardiology, pharmacy, and oncology teams. Collaboration between teams and an understanding of the risks associated with anthracyclines as well as the pharmacological strategies available to mitigate those risks allows for treatment to be delivered as safely as possible for the patient [35]. The development of an individualized approach toward anthracycline prescribing and monitoring could improve individual outcomes for patients.

5. Monitoring recommendations

Echocardiography is commonly used to detect and monitor cardiac function in this patient group. Other available modalities include nuclear imaging (multi-gated acquisition scan, MUGA) and cardiac magnetic resonance imaging. The advantages of echocardiography include being safe, readily available, and accurate. The other imaging modalities provide accuracy in measurement of LVEF, but are less readily available, more costly, and nuclear medicine imaging exposes the patient to radiation [36]. There may be a role of using other modalities if echocardiography is not suitable for an individual patient. Using the same imaging modality throughout enhances reproducibility and avoids discrepancies in reporting.

It is important to arrange baseline cardiac imaging before the patient commences treatment, and as earlier discussed, to help identify any patients at additional risk of developing cardiotoxicity. Regular monitoring throughout treatment is recommended, as well as regular review of patients receiving anthracyclines for any sign and symptoms of cardiac failure or other pathology. For patients with a baseline LVEF < 50%, anthracyclines should be used with caution, and alternative chemotherapeutic agents considered [6]. If the use of anthracycline is unavoidable, it is recommended to repeat cardiac imaging between alternate cycles of treatment [36]. Early specialist cardiology review and assessment is recommended. The role of cardioprotective medications such as dexrazoxane will be further explored and can help to reduce the risk of drug-associated cardiotoxicity.

In addition to measurement of ejection fraction, echocardiographic assessment of global longitudinal strain (GLS) allows early detection of subclinical cardiac dysfunction. As with measurements of LVEF, Plana et al. recommend baseline and follow up measurement of GLS. A relative percentage reduction of >15% in GLS is likely to be abnormal, whereas a change of <8% is unlikely to be significant [37]. Earlier identification of changes allows early intervention and collaboration between teams to optimize the patient.

Koutsoukis et al. describe early-onset cardiotoxicity as being most common, that which occurs within a year of completion of treatment, although frequently much sooner. Late-onset cardiotoxicity can occur up to 10–20 years following chemotherapy [38].

The role of monitoring beyond completion of treatment is unclear. The risk to patients is certainly present, and early detection of cardiac abnormalities may improve outcomes. Repeat imaging at the conclusion of treatment is recommended, and The European Society of Cardiology additionally recommends repeat echocardiography at 1 and 5 years after completing treatment for those patients who received greater than or equal to 300 mg/m^2 of doxorubicin or equivalent [39].

Stone et al. suggest a follow-up strategy including a repeat echocardiogram at completion and six months after treatment; and thereafter tailoring follow up to the individual patient depending on anthracycline cumulative dose exposure, individual baseline risk factors, and exposure to other cardiotoxic cancer treatments including other medications and chest directed radiotherapy [36].

Other monitoring strategies, including the use of serial biomarker measurements have been studied but their role is unclear. A rise in serum troponin-I has been associated with both symptomatic and asymptomatic cardiac dysfunction [40]. Similarly, the absence of a rise in troponin-I has been associated with no cardiac compromise.

The role of measuring Brain Natriuretic Peptide (BNP) has also been studied although its utility as a serum biomarker compared to troponin-I is unclear. As a baseline measurement, correlations were seen between LVEF < 50% and raised BNP levels, indicative of baseline poor cardiac function, although the relationship is not linear. Although out of 48 patients receiving anthracycline chemotherapy, 19% had a reduction in LVEF, there was a lack of correlation with serial changes in BNP. It is a poor predictive marker of change in cardiac function and should not replace echocardiographic monitoring [41].

The role of serum testing is less well defined as compared to imaging modalities as a surveillance option in these patients. The timing of checking serum troponin can impact the laboratory values, and the optimum strategy is not yet clear. The ESMO Guidelines recommend baseline measurement of cardiac biomarkers for high-risk patients undergoing chemotherapy with anthracyclines [6].

In the above study of 204 patients [40], the relationship between a raised troponin-I and LVEF reduction was seen. Additional work is needed to ascertain whether these are transient changes or whether this biomarker indicates a long-term risk of irreversible cardiotoxicity.

Serum biomarker testing may be a cost-effective and timely way to monitor for cardiotoxicity in our patient population receiving anthracycline chemotherapy, but further work is needed to correlate the significance and particular long-term implications of these results and as yet we are unable to rely on biochemical monitoring over cardiac imaging.

6. Pharmacological strategies

The need for strategies to reduce the risk of anthracycline-associated cardiotoxicity is clear. Early collaboration between oncologists, cardiologists, and imaging teams is imperative to early identification and management of both risk factors and toxicities that arise.

6.1. Anthracycline dosing schedules

A 2016 Cochrane Review of 11 studies evaluated differences in anthracycline infusion durations and schedules. The meta-analysis found a significant reduction in the occurrence of both clinical heart failure, and subclinical cardiac compromise, with an infusion duration of six hours or longer. There was no significant difference in the occurrence of cardiotoxicity when reviewed according to peak dosing of doxorubicin [42].

6.2. Dexrazoxane

Dexrazoxane is a cardioprotective agent useful against the toxic effects of anthracycline chemotherapy. It is an iron-chelating agent and displaces iron from anthracycline thereby inhibiting the doxorubicin-iron complexes previously discussed [43].

In addition to its role as an iron chelator, dexrazoxane acts as a topoisomerase II inhibitor and subsequently prevents the formation of anthracycline-DNA-topoisomerase II complexes [43]. The inhibition of topoisomerase IIβ by dexrazoxane interferes with the etiology of anthracycline-associated cardiotoxicity damage, thus contributing to its cardioprotective effect [22]. In vivo studies have demonstrated that dexrazoxane leads to the depletion of topoisomerase IIβ in cardiomyocytes, and a subsequent reduction in cardiac DNA damage [44].

Dexrazoxane was approved by the US Food and Drug Administration (FDA) in 1995 and is also recommended by the National Institute for Health and Care Excellence (NICE) for patients who have previously received a cumulative dose of 300 mg/m^2 doxorubicin, or alternative anthracycline equivalent, for whom further anthracycline treatment is indicated.

A systematic review and meta-analysis by Smith et al. examined the cardiotoxicity of anthracycline agents. In comparison to the administration of an anthracycline without co-administration of dexrazoxane, they found that adding dexrazoxane significantly reduced the risk of both symptomatic and asymptomatic cardiotoxicity [45].

Two multi-center randomized placebo-controlled trials assessed the role of dexrazoxane in breast cancer patients receiving beyond 300 mg/m^2 doxorubicin [46]. For the purpose of these trials, a cardiac event was defined as symptomatic heart failure, or a deterioration in LVEF from baseline by 10% to below the lower limit of normal, or a deterioration by 20% to 5% below the lower limit of normal at the individual institution. The studies found that the risk of experiencing a cardiac event was more than tripled in the group who received placebo compared to those who received dexrazoxane. The incidence of heart failure in the dexrazoxane group was 3%, compared to 22% in the placebo group. This was a statistically significant difference and highlights the utility of dexrazoxane in patients requiring higher cumulative doses of anthracycline chemotherapy beyond 300 mg/m^2 doxorubicin equivalent.

In a randomized Phase III study of the cardioprotective effect of dexrazoxane, 164 breast cancer patients being treated with further anthracyclines after previous anthracycline exposure were randomized to receive it with (85 patients), or without (79 patients) dexrazoxane. The addition of dexrazoxane led to a significant decline in the risk of developing a cardiac event as well as a significant reduction in the risk of developing congestive heart failure. This study supports the addition of dexrazoxane in patients requiring higher cumulative doses of anthracycline [47].

This finding is further supported by a randomized trial of dexrazoxane in pediatric sarcoma patients treated with doxorubicin which included 18 patients treated with dexrazoxane and 15 control patients. Those treated with dexrazoxane were significantly less likely to develop cardiotoxicity and received a higher cumulative dose of anthracycline [48].

A randomized prospective study by Lopez et al. found that the addition of dexrazoxane in patients with soft tissue

sarcoma or breast cancer being treated with epirubicin provided significant protection against the development of cardiotoxicity. 4/62 patients in the control arm (epirubicin without addition of dexrazoxane) developed congestive heart failure New York Heart Association (NHYA) Grade III or IV indicating moderate to severe impairment. NYHA Grade II (mild) cardiac impairment was seen in 9/62 additional patients in the control group and in 4/59 patients who received epirubicin with dexrazoxane [49].

A proposed limitation of dexrazoxane may be its effect on the chemotherapeutic effectivity of anthracycline. In one study, there was a significantly lower radiological response rate in the dexrazoxane arm although there was no significant difference in time to progression or overall survival [50]. None of the other randomized trials have demonstrated a significant difference in response rate, progression-free survival, or overall survival [47–49,51].

Two meta-analyses of randomized and non-randomized trials evaluating the addition of dexrazoxane to anthracycline chemotherapy in both breast cancer patients and in a pediatric population showed that the addition reduced the risk of cardiotoxicity, without detrimental impact on oncological outcome [43,52].

The cardiotoxicity experienced by patients with soft tissue sarcoma receiving doxorubicin as part of the Phase III ANNOUNCE trial was recently evaluated. The median number of cycles of doxorubicin received was 6 with a median cumulative dose of 450.3 mg/m^2. 90/506 patients received higher cumulative doses ≥600 mg/m^2. Those patients who received higher doses of doxorubicin also more frequently received dexrazoxane in addition. Of the 90 patients receiving a cumulative dose ≥600 mg/m^2, 81 also received dexrazoxane. This analysis showed that approximately 50% of patients had a decrease in LVEF, however the rates of clinical cardiotoxicity were low, observed in approximately 1% of patients. Reductions in LVEF in patients receiving higher doses of doxorubicin (≥450 mg/m^2) were not significantly impacted by the addition of dexrazoxane. These findings support the use of increased cumulative doses of anthracycline chemotherapy when used in addition with dexrazoxane for cardioprotection [53].

Tebbi et al. studied the addition of dexrazoxane to standard of care regimes in a pediatric population receiving treatment for Hodgkin's Lymphoma [54]. At the four year follow up, eight patients who had received dexrazoxane developed a secondary malignancy. Six patients developed acute myeloid leukemia or myelodysplastic syndrome, one thyroid carcinoma and one osteosarcoma. It is difficult to ascertain whether the addition of dexrazoxane increased the risk of a secondary malignancy, and other similar studies have identified this as being a rare event [55]. Further work has refuted the hypothesis of dexrazoxane increasing the risk of second malignancies [56], with a large retrospective review of 15,532 cases demonstrating no increased risk of secondary acute myeloid leukemia in pediatric patients who had been treated with dexrazoxane [57]. Overall, there is a lack of clinical evidence to support the suggestion that co-administration of dexrazoxane increases the risk of developing a second malignancy.

A 2011 meta-analysis of cardioprotective agents for patients being treated with anthracyclines reported on myelotoxicity associated with dexrazoxane. There was a significant increase in incidence of Grade 3 or 4 anemia and reduced white blood cell count in the patients treated with dexrazoxane in addition to anthracycline as compared to the control group [58]. This is supported by a 2019 single-center retrospective review of 133 patients with soft tissue sarcoma receiving anthracycline with or without dexrazoxane in addition, whereby a significant increase in the incidence of myelosuppression was seen in the dexrazoxane group [59].

The benefits of dexrazoxane and its unique approval in the management of anthracycline-associated cardiotoxicity represent significant milestones for patients in this cohort. Overall, we propose that the careful consideration and use of dexrazoxane in patients who are high risk for cardiotoxicity, or who require high cumulative doses of anthracyclines, is an important addition with benefit to patients.

6.3. Liposomal doxorubicin

Liposomal preparations of drugs allow the modification of pharmacokinetics and distribution whilst aiming to reduce toxicity, often also allowing an increased amount of drug to be delivered to tumor cells whilst reducing exposure of healthy tissue [60].

The use of liposomal doxorubicin reduces the potential cardiotoxicity from anthracyclines. The pharmacokinetics and distribution of encapsulated doxorubicin is different, and there is decreased uptake in normal tissues [61].

There are two available preparations of liposomal doxorubicin, non-pegylated (Myocet®) and pegylated liposomal doxorubicin (Caelyx®, Doxil®). The liposomal preparations permeate cells in areas where there is vascular disruption and inflammation. In contrary, the myocardial vascular supply has tight junctions and endothelial barriers. As such, the drug would not permeate the cardiac tissue but tumor exposure would be maintained. The encapsulation of doxorubicin by the pegylated liposomes causes the serum half-life to be significantly prolonged and therefore the drug remains in circulation for a longer period of time and is released more slowly, entering into tumors via leaky vasculature. Encapsulated drug entering the myocardium would not be expected to cause cardiotoxicity due to lack of bioavailability. The plasma levels of free doxorubicin with these preparations are low, and thus conventionally seen anthracycline toxicity is rare [61].

Smith et al. described that as compared to conventional doxorubicin, liposomal doxorubicin significantly decreased the risk of both symptomatic and asymptomatic cardiotoxicity as well as any cardiotoxic event. There was no statistically significant difference when liposomal doxorubicin was compared to epirubicin. The same review found no significant difference between response rate or survival between liposomal and conventional doxorubicin [45].

Compared to other anthracycline agents, liposomal doxorubicin is costly and therefore not routinely recommended as an anthracycline substitute unless specially indicated [62]. Its use is however approved by the National Institute for Health and Care Excellence (NICE) as monotherapy for patients with metastatic breast cancer who are at increased cardiac risk.

Currently, liposomal doxorubicin is indicated in HIV-related Kaposi's sarcoma with Phase II/III data demonstrating a higher response rate and less toxicity when compared to alternative chemotherapy agents, including conventional doxorubicin [63].

A meta-analysis evaluating the safety and toxicity of liposomal doxorubicin in comparison to conventional anthracyclines showed a more favorable toxicity profile with the liposomal preparations [64]. The lower incidence of congestive heart failure, alopecia, neutropenia, and thrombocytopenia all support the use of liposomal doxorubicin in patients vulnerable to cardiotoxic adverse effects or those with prior anthracycline use.

A randomized trial of liposomal doxorubicin versus conventional doxorubicin assessed cardiotoxicity in 224 patients with metastatic breast cancer being treated in the first-line setting [65]. Cardiotoxicity was observed in 13% of patients treated with liposomal doxorubicin, and 29% of those treated with conventional doxorubicin. The median cumulative dose of doxorubicin at onset of cardiotoxicity was 785 mg/m^2, which is higher than previously discussed thresholds used most commonly in clinical practice. There was no significant difference in antitumor activity between the study groups.

6.4. Aldoxorubicin

Novel anthracycline analogues may provide alternative emerging treatment options for this cohort of patients. Aldoxorubicin is an intravenous prodrug formulation of doxorubicin with promising safety profile and reduction in cardiotoxic effects as compared to doxorubicin [66]. Data from a Phase II open-label trial for patients with soft tissue sarcoma demonstrated superiority of aldoxorubicin over doxorubicin with tumor response in 63% of the aldoxorubicin arm, and 41% in the doxorubicin arm. The PFS was 5.6 months for the aldoxorubicin cohort, and 2.7 months for the doxorubicin cohort. However, these results were not shown to be statistically significant. In the study time period, no acute cardiotoxic effects were seen in either group, although 3/40 patients in the doxorubicin arm had a reduction in LVEF to <50% [67].

A Phase III study of aldoxorubicin in soft tissue sarcomas randomized patients to either receiving investigators choice chemotherapy or aldoxorubicin [68]. Although response rate, progression-free and overall survival were not improved, it is interesting to note that higher doxorubicin equivalent doses of aldoxorubicin were able to be used with no increase in clinical cardiotoxicity [69].

The ongoing study and development of novel anthracycline preparations is an exciting prospect for the future of patients who rely heavily on the use of anthracycline chemotherapy for their disease. The administration of higher cumulative doses with similar antitumor profile and fewer cardiotoxic effects may lead to improved outcomes for these patients for whom the treatment options are often limited.

6.5. Primary and secondary prevention strategies

Primary prevention strategies aim to prevent cardiotoxicity at the time of, or prior to, treatment. Earlier discussed modifiable risk factors include obesity, smoking, inactivity, diabetes, and hypertension and are important to address.

Early consideration of the use of the cardioprotective agent dexrazoxane is relevant in patients identified as high risk of developing cardiotoxicity [70].

A systematic review and meta-analysis of primary prevention strategies reviewed the addition of treatment with dexrazoxane, beta-blocker, statin, or angiotensin receptor blockers (ARB) in patients with a normal baseline LVEF and no history of heart failure. This meta-analysis found the use of statins, beta-blockers, and ARBs to be beneficial in preventing anthracycline-associated cardiotoxicity. The authors highlighted the need for further studies to compare the role of using these medications upfront versus targeting treatment depending on the development of cardiotoxicity [71].

A Phase III multi-center study evaluated the use of angiotensin-converting enzyme (ACE) inhibitor (enalapril) as a preventative measure. Patients were randomized to either receive enalapril upfront alongside cardiotoxic chemotherapy, or to only start enalapril after a rise in serum troponin levels. After 1 year, only 3/273 patients developed cardiotoxicity (LVEF < 50%), with no significant difference seen between groups. The study suggested that the use of enalapril as primary prevention did not improve outcomes as compared to commencing it in response to signs of cardiac stress [72].

There is a lack of strong evidence for the use of medication upfront as primary prevention strategies; however, there is clear benefit to the use of dexrazoxane in patients with established or at risk of poor cardiac function. The balance of primary prevention with pharmacological strategies needs to be balanced against side effects associated with medication [70].

Secondary prevention involves the management of asymptomatic anthracycline-associated cardiotoxicity and the prevention of symptoms and progression. The lack of clear evidence and consensus guidelines presents challenges to physicians in managing this cohort of patients.

The treatment of anthracycline-associated cardiotoxicity requires a multidisciplinary approach and has improved with the development of specialist cardio-oncology clinics. The management may include pharmacological intervention including ACE inhibitors, beta-blockers, and diuretics as well as early intervention for modifiable risk factors [7]. The importance of collaboration between cardiologists and oncologists was highlighted by Yoon et al., who identified that for a cohort of patients receiving either anthracycline or trastuzumab therapy, only 42% of those with an asymptomatic decrease in LVEF were referred for a cardiology consultation [73].

Cardinale et al. studied the impact of pharmacologic therapy on patients with anthracycline-associated cardiotoxicity and found that in patients with a decrease in LVEF ≤45%, treatment with enalaparil and carvedilol resulted in a normalization of LVEF in 42% of the patients [74]. In addition to the use of enalapril and carvedilol, diuretics, anticoagulants, and anti-arrhythmics were prescribed at the discretion of the cardiologist in line with standards of care.

We have previously discussed the importance of screening and early detection of cardiotoxicity in patients treated with anthracyclines. The cumulative incidence of cardiotoxicity was highest at one year post treatment completion, although we have seen that the late-onset cardiotoxicity can also be debilitating even decades later.

7. Expert opinion

Anthracyclines are important agents in the treatments of many different cancer types. Drug-related cardiotoxicity is the main limiting factor in the delivery of higher doses of anthracyclines.

Long-term survival rates from cancer are improving, and the sequalae of previous treatment effects may be more evident as cancer patients live longer. Despite advances in cancer treatments, anthracyclines are likely to remain a standard of therapy for a number of cancer types, both across the adult and pediatric groups.

Addressing anthracycline-associated cardiotoxicity has particular significance for pediatric cancer survivors, as it remains a major cause of morbidity and mortality in this population [75].

Anthracyclines are not unique in having cardiotoxic side effect profiles. They have been in use for a long time, and still are a critical backbone in many cancer treatments. However, amongst others, drug classes such as tyrosine kinase inhibitors, anti-HER2 therapies, and immunotherapy agents can all also have various cardiotoxic effects. The need for strategies to identify and manage cardiotoxicity in cancer patients is growing, and more data are needed on long-term risks in these patients as well as both primary and secondary prevention strategies – inclusive of both pharmacotherapeutics and modifiable lifestyle recommendations. The prevention of treatment-associated cardiotoxicity and early collaboration between specialty teams is paramount. Accurate assessment of baseline characteristics and risk factors allows an individualized approach to modifying each patient risk [76].

Both primary and secondary prevention strategies are important. Secondary prevention should be initiated early, when signs of cardiac dysfunction are present even in the asymptomatic patient. The use of pharmacological strategies as primary prevention in patients without cardiac compromise or symptoms remains less convincing, and the side effect profiles of medications must be balanced against the patient's individual risks.

There are promising advances in pharmacological strategies, both in the use of cardioprotective agents such as dexrazoxane to prevent the development of cardiotoxicity; but also in the development of alternative anthracycline formulations with similar oncological profile but lower cardiotoxic effects. There are encouraging data supporting the use of higher cumulative doses of anthracyclines with careful monitoring and management of cardiotoxicity, and this may improve options for patients who respond to anthracycline but are currently limited by cumulative dosing guidelines.

Early detection of anthracycline-associated cardiotoxicity with referral to cardio-oncology clinics may improve outcomes for these patients. Further work regarding appropriate long-term monitoring strategies for patients who have completed anthracycline chemotherapy will help best identify those at long-term risk many years after completion of treatment. The use of biomarkers presents an interesting avenue for more readily available ways to monitor patients for a decrease in cardiac function, but as yet cannot be recommended in place of established monitoring studies.

We recommend a multi-disciplinary approach to the care of these patients. The emerging and growing cross-specialty working between cardiologists and oncologists will enable early identification of patients most at risk, early management of risk factors, and pharmacologic intervention. The use of screening tools including pharmacogenomic prediction models and baseline serum biomarker testing require further research but is an exciting avenue to develop in the future to enable a more individualized approach for each patient. Long-term survival clinics are of particular importance for the pediatric population and consensus guidelines for regular screening for cancer survivors will help to provide a coordinated approach across different centers.

Taking the above recommendations into account, we hope that we can move to employing an evidence-based personalized approach to identifying and managing the patients most affected by, or at risk of, anthracycline-associated cardiotoxicity. Prompt intervention will improve outcomes and enable patients to continue to safely receive their anti-cancer therapy.

Declaration of interest

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ORCID

Anna Stansfeld http://orcid.org/0000-0001-8385-2046

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