Primary Prevention Strategies for Anthracycline Cardiotoxicity: A Brief Overview

Pierantonio Menna a Emanuela Salvatorelli b

a Clinical Pharmacology Unit and b Department of Medicine, Campus Bio-Medico University Hospital, Rome, Italy

Introduction

Doxorubicin (DOX) and other antitumor anthracyclines, e.g., epirubicin (EPI), daunourubicin, and idarubicin, are widely used to treat many solid or hematologic malignancies; however, the clinical use of anthracyclines is limited by their severe cardiotoxicity, which correlates with the cumulative administered dose. In fact, anthracyclines induce cardiotoxicity that may progress toward dilated cardiomyopathy and systolic heart failure (HF). In the case of DOX, the risk of HF averages 5% at a cumulative dose of 400 mg/m² but increases exponentially at higher doses [1]. Interestingly, however, studies of childhood and adult cancer survivors suggest that HF may occur also after cumulative doses <400 mg/m². Moreover, patients exposed to reportedly safe doses of anthracyclines may develop cardiomyopathy and HF any time after cancer diagnosis and treatment [1, 2]. These findings suggest that there may be no safe dose of anthracyclines [3].

This having been recognized, clinicians should consider adequate measures of prevention for patients who are candidates for cumulative anthracycline doses [1, 4]. Postchemotherapy surveillance is also needed to detect...
subclinical or mild asymptomatic cardiotoxicity before it progresses toward HF.

Here, we briefly review the potential strategies for preventing anthracycline cardiotoxicity.

Primary Prevention of Anthracycline Cardiotoxicity

Pharmacokinetic Manipulations of Cardiac Exposure to Anthracyclines

Anthracycline cardiotoxicity is a complex, multifactorial process that involves many potential molecular players [5]. Pharmacokinetic determinants of cardiotoxicity are relatively more obvious. For example, cardiotoxicity is reduced by replacing bolus administration with slow infusions over 24–96 h. This approach is based on an apparent dissociation between the pharmacokinetic determinants of anthracycline anti-tumor activity versus cardiotoxicity. Whereas anthracycline activity correlates with total plasma exposure to anthracyclines, as exemplified by the area under the curve (AUC), cardiotoxicity correlates with the peak plasma level of anthracyclines (Cmax) and their penetration into cardiac tissue [6]. Substituting slow infusion for bolus administration does not significantly affect AUC, but it diminishes Cmax and anthracycline accumulation in the heart [6, 7]. The activity and cardiac safety of slow anthracycline infusions have been documented in numerous studies. In some settings, slow infusions actually allowed for administering anthracyclines in cumulative doses otherwise known to induce HF [6]. The advantage of replacing bolus administration with slow infusion is nonetheless counterbalanced by the patient’s discomfort due to prolonged hospitalization and the exacerbation of exposure effects such as myelotoxicity, mucositis, and alopecia. Moreover, slow infusions do not always prevent the risk of HF in survivors of childhood acute lymphoblastic leukemia [8].

Another possible concern originates from studies on breast cancer patients treated with DOX slow infusions. These patients developed an increased accumulation of DNA-oxidized bases in their peripheral blood mononuclear cells [9]. This may have been the consequence of prolonged exposure to oxidative stress that is caused by the redox cycling of anthracyclines [6]. Should DNA damage also occur in cardiomyocytes and, more notably, in cardiac stem cells that are committed to repopulate the cardiac foci of anthracycline-induced damage, patients treated with anthracycline slow infusions would still carry a risk of developing HF [10]. Should DNA damage occur in hematopoietic precursors, this might also introduce an increased risk of secondary hematologic malignancy [6, 10].

The pharmacokinetic determinants of anthracycline cardiotoxicity are nonetheless liable to other manipulations and strategies for reducing cardiac exposure to anthracyclines. Cardiotoxicity can, in fact, also be reduced by replacing conventional anthracyclines with liposome-encapsulated ones. Two liposomal formulations have been approved for use with certain defined clinical indications. One liposomal DOX (Caelyx® in Europe and Doxil® in the USA) has polyethylene glycol embedded in the lipid layer; other formulations of DOX (Myocet®) or daunorubicin (DaunoXome®) adopt uncoated liposomes.

In brief, liposomal anthracycline formulations are too big to cross the gap junctions of endothelial linings in the heart and many other healthy tissues [11, 12]. Steric hindrance limits anthracycline diffusion in extravascular compartments, which results in a higher Cmax and a lower distribution volume and clearance of liposomal formulations compared to conventional anthracyclines; however, the majority of circulating anthracycline remains embedded in the liposomal vesicle [13]. This reasoning anticipates that patients treated with liposomal anthracyclines would be exposed to very low levels of a circulating “free” drug, which eventually minimizes the risk due to cardiac exposure to freely diffusible anthracycline [6]. Liposomal formulations are nonetheless small enough to cross the very irregular and leaky microvasculature that characterizes solid tumors [6]. Following extravasation in tumors, liposomal formulations accumulate by virtue of processes that include the insufficient lymphatic drainage and increased interstitial pressure that also characterize many tumors. This is the so-called “enhanced permeability and retention effect” [13]. Moreover, the tumor microenvironment shows the potential for destabilizing the liposomal vesicle. This may occur through such diverse mechanisms as low pH, the release of lipases from necrotic tumor cells, or the release of oxidizing agents from tumor-infiltrating inflammatory cells. Resident macrophages could contribute to the degradation of liposomal vesicles and release free anthracyclines, but the actual weight of this mechanism is uncertain [13, 14] (Fig. 1).

Preclinical studies showed that liposomal formulations deliver substantial amounts of anthracycline in tumors while also delivering much smaller amounts of DOX in cardiac tissue compared to conventional DOX [13]. In some animal models, liposomal formulations actually expose tumor cells to higher amounts of free anthracycline than conventional formulations do [13]. For many reasons, liposomal anthracycline formulations might be considered prototypic examples of “targeted” drugs [10].
Many clinical studies show that liposomal anthracyclines are active and safe. A Cochrane analysis identified liposomal anthracyclines as the only formulations able to reduce the risk of anthracycline-related cardiotoxicity [15]. The efficacy and cardiac safety of liposomal DOX has been documented also under very unfavorable clinical conditions, e.g., when there is concomitant administration of DOX and the anti-ErbB2 monoclonal antibody, trastuzumab. Concomitant administration of conventional DOX and trastuzumab would precipitate serious cardiac events in women with ErbB2-overexpressing breast cancer, presumably because trastuzumab diminishes cardiac defense mechanisms against anthracycline injury [12]. In contrast, both uncoated and pegylated liposomal DOX could be safely administered with concomitant trastuzumab [16, 17], demonstrating that the limited cardiac penetration by the liposomal anthracycline prevented toxic synergism between trastuzumab and DOX.

Liposomal anthracyclines have been investigated in relatively few registration-oriented randomized trials. This means that liposomal formulations are approved for use only with limited clinical indications, e.g., metastatic breast cancer (uncoated liposomal DOX), metastatic breast cancer, advanced/refractory ovarian cancer, multiple myeloma, and AIDS-related Kaposi sarcoma (pegylated liposomal DOX), and AIDS-related sarcoma (liposomal daunorubicin) [1]. All other indications remain investigational, but clinicians should consider using liposomal anthracyclines, at least for patients who present at cancer diagnosis with cardiovascular risk factors (preexisting cardiac disease, arterial hypertension, diabetes, etc.) that are known to aggravate the risk of HF from conventional anthracyclines.

**Pharmacodynamic Approaches for Cardiac Prevention**

For a long time, replacing a given anthracycline with an equiactive but less cardiotoxic analog has been considered the optimal and most obvious approach for preventing cardiotoxicity. Even though many anthracycline analogs have been tested preclinically and in early clinical studies, the search for a “less cardiotoxic” anthracycline has proven difficult, and unambiguous clinical validation of such an anthracycline is lacking. This probably reflects the multifactorial nature of anthracycline cardiotoxicity and the difficulties in disentangling the pharmacodynamic characteristics that eventually make one anthracycline less cardiotoxic than another.

DOX and other anthracyclines approved for clinical use share a tetracyclic quinone-hydroquinone moiety, an aminosugar (daunosamine), and a short side-chain with a carbonyl group. The quinone group undergoes a 1-electron reduction which forms a semiquinone radical. This quickly regenerates the parent quinone by reducing molecular oxygen to superoxide anion (O\textsuperscript{2}–), and dismutation of the latter generates hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}). Thus, continued redox cycling of the quinone moiety exposes cardiomyocytes to reactive oxygen species (ROS) that, in concert with iron, may cause oxidative stress. To the extent that cardiomyocytes are relatively deficient in oxyradical-scavenging enzymes, such as superoxide dismutase and catalase, or glutathione peroxidase, the up-regulation of oxidative stress might be highly deleterious to the heart [18, 19]. In addition, the carbonyl group in the side-chain has been implicated to explain the mechanism or mechanisms of cardiotoxicity. In fact, 2-electron reduction of the carbonyl group generates a secondary alcohol metabolite that is significantly more polar than its parent anthracycline. This long-lived anthracycline metabolite contributes to inducing oxidative damage but can...
also cause oxidant stress-independent mechanisms of toxicity, e.g., the inhibition of numerous ATPases [21] or the activation of iron-regulatory proteins that control the cellular uptake and storage of iron [22, 23] (Fig. 2).

The possible role of ROS and/or secondary alcohol metabolite in the pathogenesis of anthracycline-related cardiomyopathy and HF may or may not correlate with the clinical facts [6]. EPI, which differs from DOX by the epimerization of a hydroxyl group in daunosamine, shows a defective conversion to ROS and secondary alcohol metabolite [24]. And, not surprisingly, EPI is often said to be less cardiotoxic than DOX. Interestingly, however, the reduced cardiotoxicity of EPI versus DOX is only evident when they are given in equal amounts. Under such conditions, EPI shows a higher body clearance and a reduced antitumor activity. Should EPI be administered in higher doses to compensate for elimination and to attain the same activity as DOX, which is common practice in adjuvant therapy for breast cancer, the HF risk increases [25]. EPI would nonetheless retain advantages over DOX if the 2 were to be combined with tubuline-active poisons like taxanes, also common in adjuvant therapy of breast cancer. Taxanes, like paclitaxel and docetaxel, can in fact bind to a regulatory site of the reductases that convert anthracyclines to secondary alcohol metabolites, and, by doing so, they have been shown to increase DOX reduction to its metabolite, doxorubicinol. This does not occur with EPI, which, in principle, may result in an improved cardiac tolerability of EPI-taxane regimens compared to DOX-taxane regimens [26]. Amrubicin and the novel anthracenedione, pixantrone, also show a defective conversion to ROS and/or secondary alcohol metabolite [27, 28]. Unfortunately, both of these drugs are approved for use only under limited conditions, and comprehensive clinical comparisons with DOX or other anthracyclines are limited [1]. Pixantrone was less cardiotoxic than DOX in a phase II study on patients with newly diagnosed non-Hodgkin lymphoma [29]. Pixantrone was also reasonably cardiac-tolerable in patients with refractory/relapsed non-Hodgkin lymphoma that had been previously treated with DOX [30]. Again, this might identify pixantrone as one of the long-sought "less cardiotoxic" anthracyclines. This having been said, it is worth noting that the mechanisms of antitumor activity of pixantrone are substantially different from those of DOX and other anthracenediones, which suggests that pixantrone should not be grouped with anthracycline-like drugs [31, 32].
Other strategies for reducing anthracycline cardiotoxicity have been based on the coadministration of drugs or natural compounds that fortify cardiomyocyte defenses against oxidative stress. Exploratory clinical trials that probed the protective efficacy of high-dose vitamin E or N-acetylcysteine were uniformly disappointing [33, 34]. In nononcologic patients, less robust interventions with vitamin E would be sufficient to prevent or attenuate the incidence of cardiac events that presumably involve oxidative stress, e.g., nonfatal myocardial infarction in patients with coronary atherosclerosis, arrhythmias, reinfarction after aortocoronary bypass, and fatal infarction in smokers [35]. How can these discrepancies be reconciled in a cohesive picture? In the case of anthracycline-related cardiotoxicity, one might speculate that antioxidants fail to reach critical levels in cell “sanctuaries” exposed to oxidative stress. Alternatively, continued redox cycling of the quinone moiety does expose cardiomyocytes to oxidative stress, but this is relatively unimportant for the occurrence of cardiotoxicity [10, 35].

The only drug that has proven protective in preclinical and clinical settings is dexrazoxane (DRZ). This is a bis-ketopiperazine which diffuses in cardiomyocytes, undergoes stepwise hydrolysis of its piperazine rings, and releases a diacid diamide (code-named ADR 925) that is similar to EDTA and chelates iron before it converts O$_2^-$ and H$_2$O$_2$ into more potent hydroxyl radicals or equally reactive iron-oxygen complexes [35]. The myocardial uptake of DRZ is extraordinarily rapid and approaches its maximum level within 1 min, which anticipates a rapid exposure of cardiomyocytes to ADR 529 [36]. This is particularly relevant for clinical conditions when DRZ is infused just prior to the anthracycline. This having been said, how is it that cardiotoxicity could be prevented by DRZ but not antioxidants? Both compounds should be cardioprotective if one assumes that iron-catalyzed oxidative stress was involved [35]. Such a discrepancy needs to be addressed by considering the broad spectrum of anthracycline targets in tumors and cardiac cells.

The antitumor activity of anthracyclines builds on the formation and stabilization of a reaction intermediate in which DNA strands are cut and covalently linked to tyrosine residues of topoisomerase IIα. This reaction negates the resealing of DNA and leads to the formation and accumulation of protein-capped DNA double-strand breaks. Topoisomerase IIα-mediated DNA damage is then followed by cell growth arrest in G1 and G2, and programmed cell death eventually occurs [6]. Whereas topoisomerase IIα is expressed primarily in tumor cells and normal proliferating cells, cardiomyocytes and other quiescent normal cells express constitutive levels of a β-isoform of topoisomerase II that is also inhibited by anthracyclines. Anthracycline inhibition of topoisomerase IIβ causes DNA double-strand breaks and cardiomyocyte death [37]. Topoisomerase IIβ therefore represents a previously unrecognized and probably a major target of anthracycline cardiotoxicity. DRZ can compete for the ATP-binding site of topoisomerase IIβ, and, by so doing, it forces topoisomerase IIβ to assume a closed-clamp configuration that precludes the formation of anthracycline-DNA-topoisomerase IIβ complexes [38]. DRZ therefore prevents DNA damage and cardiomyocyte death [37, 38] (Fig. 3).

How can these notions help to reconcile the lack of protection by antioxidants with the efficient protection provided by DRZ? The main conclusion to be drawn is that iron chelation and the mitigation of oxidative stress might not represent the only or prevailing mechanism of cardioprotection by DRZ. Accordingly, it was found that there was marginal protection or lack of effect when anthracycline-treated animals were exposed to DRZ analogs that chelated iron but did not inhibit topoisomerases [39]. Likewise, new and more potent compounds, designed to intensify iron chelation and redox-inactivation, have failed to provide equal or better cardiac protection than DRZ [40, 41].

DRZ has prevented anthracycline-related cardiotoxicity in many clinical studies of both childhood and adult cancer patients, often allowing for anthracyclines to be administered in cumulative doses known to induce HF [42]. DRZ is the only drug to be approved by the US FDA for use as a cardiac protectant in patients exposed to anthracyclines. Regrettably, however, the clinical use of DRZ is limited by just 1 report of its possible interference with anthracycline activity in metastatic breast cancer [43]. An interference of DRZ with anthracycline activity, possibly mediated by DRZ binding to topoisomerase IIα [44], might, at least in principle, justify concerns about its negative influence on tumor response, but a plethora of studies now demonstrates that such interference does not occur or is clinically unimportant [45]. In spite of such compelling evidence, the American Society of Clinical Oncology, Chemotherapy, and Radiotherapy Expert Panel maintains a cautionary position and recommends using DRZ only under very limited conditions (e.g., patients who have received >300 mg/m$^2$ of DOX for metastatic breast cancer and who may benefit from continued anthracycline treatment) [46].

The clinical use of DRZ has also been limited by concerns about an increased risk of second malignancies [47]. This was observed in survivors of young-adolescent Hodgkin lymphoma who had been treated with DOX in com-
bination with etoposide. Such concerns need to be interpreted by considering that etoposide is also a general topoisomerase inhibitor, and so patients exposed to DOX-etoposide-DRZ combinations were actually receiving a cocktail of 3 topoisomerase inhibitors. Genetic instability may well have featured in these patients [10, 47]. It was because of such concerns that the European Medicines Agency released a formal warning to contraindicate DRZ for use in children. However, as was the case about concerns about interference with antitumor activity, claims about an increased risk of secondary malignancy have been mitigated in several reports [48–50]. Risk-benefit analysis and pharmacological reasoning therefore support an unrestricted clinical use of DRZ in children and adolescents, with the only exception being those few patients who are candidates for etoposide-anthracycline combinations [51]. It is hoped that the European Medicines Agency will soon revise its position against using DRZ in children.

Pharmacogenetic Prevention

Some patients show a predisposition to develop HF. Predisposition means that cardiomyopathy progresses and HF develops even if patients were given cumulative anthracycline doses that were thought to be safe. In the case of DOX, this would be the case for patients treated with a maximum of 240–300 mg/m² (vs. a 5% risk dose that is currently approximated to 400 mg/m²) [1]. Predisposition also means that cardiotoxicity may surface regardless of whether the patients presented at treatment with cardiovascular risk [52, 53].

It is now evident that many genetic modifiers can accelerate the course of development of anthracycline cardiotoxicity. One of the best known examples pertains to anthracycline secondary alcohol metabolites. In preclinical studies, mice with cardiac-specific overexpression of type 3 carbonyl reductase (CBR) exhibited an increased conversion of DOX to its secondary alcohol metabolite and an accelerated course of development of cardiomyopathy [54]. Conversely, mice with genetic deletion of type 1 CBR (CBR1) formed smaller amounts of alcohol metabolite and showed a reduced cardiotoxicity [55]. In clinical settings, a retrospective study of childhood cancer survivors showed that homozygosis for the gain-of-function CBR3 V244MG allele increased the risk of developing HF after low-to-moderate doses of anthracyclines [56]. Moreover, elevated expression of

Fig. 3. Dual mode of action of dexrazoxane: it may prevent cardiotoxicity by inhibiting topoisomerase IIβ, which is constitutively expressed in cardiomyocytes, or by chelating iron through its diacid diamide product of hydrolysis, ADR 529.
CBRI may well explain the higher-than-expected rates of HF that occur in individuals with Down syndrome [57, 58].

Anthracycline conversion to secondary alcohol metabolites can be mediated by other enzymes as well. Inhibitor studies would in fact suggest that aldehyde reductases also contribute to generating anthracycline secondary alcohol metabolites in the human heart [59], but information about gain-of-function genetic variants of these distinct reductases is scant at this point in time.

Individual predisposition to anthracycline cardiotoxicity can also build on high expression levels of topoisomerase IIβ [60] or genetic variants of topoisomerase IIβ coregulating factors (retinoic acid receptor-γ) [61], polymorphisms of drug transporters that contribute to anthracycline distribution and elimination (ATP-binding cassette proteins of the multidrug resistance proteins family) [62], prooxidant enzymes (NADPH oxidase) [63], and matrix-remodeling enzymes (type 3 hyaluronan synthase) [64]. In brief, a constellation of factors may cause an unpredictable aggravation of cardiotoxicity.

Can genotyping be considered a novel strategy of primary prevention? The answer is positive on conceptual grounds but negative on practical grounds. Given the multifactorial nature of cardiotoxicity, each patient should be genotyped for ≥5 potential predisposing factors. Screening for just 1 or 2 candidate genes would expose patients and doctors to false-negative information. On the other hand, recommendations about avoiding anthracyclines or reducing anthracycline dosages in patients with genetic predisposition should be supported by large prospective studies, which are not available at this point in time. This is an area of investigation that clearly needs to be developed.

**Cardiovascular Prophylaxis**

Primary prevention of anthracycline cardiotoxicity should also involve common sense procedures that apply to any patient at risk for cardiac events. Preexisting comorbidities (hypertension, systolic dysfunction, or metabolic disorders) or unfavorable lifestyle choices (smoking, overweight, or reduced physical activity) should be rigorously corrected as they have long been known to increase the risk of cardiotoxicity in patients exposed to anthracyclines [6]. Given that cardiotoxicity may occur any time after treatment with anthracyclines, and having emphasized that many genetic modifiers may increase the risk of developing HF, one should also ask whether cardiovascular prophylaxis is to be recommended also for patients without risk factors. This is a matter of debate as many doctors believe that, in low-risk patients, discomfort from antitumor drugs (nausea, vomiting, and asthenia) should not be compounded by discomfort from cardiovascular drugs (bradycardia, hypotension, fluid retention, and cough) [20]. Here, we first describe the available evidence for primary prevention with cardiovascular drugs, and then the risk versus benefit of adopting this measure.

Significant cardiac protection, measured as preservation or a limited decrease in left-ventricle ejection fraction (LVEF), was seen in studies of carvedilol (a1 and β1–2 adrenoceptor blocker) [65], nebivolol (β1 blocker) [66] or carvedilol in combination with the angiotensin-converting enzyme inhibitor, enalapril [67]. A reduced degree of protection was documented with metoprolol (β1 blocker) or enalapril alone [68]. In a recent study, the angiotensin II receptor blocker, candesartan, prevented the decline of LVEF in breast cancer patients receiving adjuvant anthracycline with or without subsequent trastuzumab. Metoprolol was ineffective in these patients [69]. Are these studies persuasive enough to recommend cardiovascular prophylaxis in any patient candidate for anthracyclines? As was mentioned for genotyping, this is one of those cases when the pros and cons need to be discussed on conceptual and practical grounds. We suggest that, conceptually speaking, there is no obvious obstacle to medicating patients candidate for anthracyclines, as the risk of HF is high enough to recommend that all cautionary measures be put into action. On practical grounds, protection with inhibitors of the renin-angiotensin system is feasible, cost-convenient, and very well characterized in terms of safety and compliance. One should have reservations if one looks at the robustness of the available studies, however. These were of a limited sample size and the protocol-specified end points often focused on marginal decrements of LVEF (e.g., ≥5% on MRI) [69]. Moreover, the available studies had no long-term follow-up, and so we do not actually know if primary prevention extends its beneficial effects in long-term survivors, who carry an increased risk of HF. When examined in a broader perspective, these reservations also raise questions as to whether primary prevention should be confined to a limited time interval or prolonged indefinitely. Having acknowledged that anthracyclines accumulate in cardiac tissue and prime patients to a lifetime risk of HF, we would suggest that pharmacologic cardioprotection should also be extended over time.

Other drugs merit consideration in the setting of primary prevention. An observational clinical cohort study of breast cancer patients treated with anthracyclines suggested that statins could also reduce the risk of HF [70]. This find-
ing appears consistent with the hitherto known cardioprotective effects of statins, such as the activation of nitric oxide synthase [71] and the opening of mitochondrial ATP-sensitive potassium channels [72]. The protective effects of statins are nonetheless most evident in patients who receive other cardiovascular drugs for preexisting risk factors. This raises questions as to whether the effects attributed to statins are actually due to the concomitant drugs or reflect the pleiotropic cardioprotective effects of statins in isolation, or in concert, with, for example, β blockers or inhibitors of the renin-angiotensin system.

One last point for consideration pertains to the dosage of cardiovascular drugs. We do not know whether drugs should be given in “prophylactic” doses tailored to the characteristics of cancer patients and to the cumulative anthracycline dose, or in “therapeutic” doses similar to those recommended for the general population. Prospective randomized trials are needed to define the efficacy and dose relations of primary prevention with cardiovascular drugs. Main strategies for primary prevention of anthracycline cardiotoxicity are summarized in Table 1.

## Conclusion

Modern oncologists and hematologists know how to use anthracyclines. The cumulative doses used in the past are now replaced by lower cumulative doses that retain activity but have a lower risk of HF. Dose reductions actually represent the first and most obvious strategy of primary prevention. We have discussed how HF may nonetheless still occur in both low- and high-risk patients.
Prevention of Anthracycline Cardiotoxicity

References

7. We have no conflicts of interest to declare.

We call attention to opportunities for primary prevention that protect the heart before it develops clinically evident damage. Secondary prevention, guided by the early symptoms or laboratory findings of cardiomyopathy (e.g., echocardiographic abnormalities or increased levels of circulating biomarkers like troponin or natriuretic peptides), would still be appropriate, but is conceptually less effective. Some potential measures for primary prevention, like liposomal anthracycline or DRZ administration, should be given greater consideration.

Disclosure Statement

We have no conflicts of interest to declare.


