

Preventing the cardiotoxic effects of anthracyclines: from basic concepts to clinical data

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Abstract

Anthracyclines are among the most active and broad-spectrum antineoplastic agents used in the treatment of several cancers. Unfortunately, the cardiac toxicity of this group of drugs, resulting in a cardiomyopathy with irreversible congestive heart failure and high mortality, is one of the main factors that limit their use. The molecular mechanisms explaining the cardiotoxicity of anthracyclines are complex, but it appears that the induction of an oxidative stress within myocardial tissue constitutes a common denominator. Some promising new strategies to reduce the production of reactive oxygen species and protect the function of the heart are now available for the treatment of patients in order to lessen the myocardial injury associated with anthracyclines.

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Introduction

Anthracyclines are among the most active and broad-spectrum antineoplastic agents used in the treatment of several cancers, such as solid tumors, leukemias, and lymphomas. Unfortunately, the conventional and cardiac toxicities of anthracyclines are among the main factors that limit their use. Clinically, the cardiotoxicity results in a cardiomyopathy with irreversible congestive heart failure and a high mortality.

Basic concepts

The molecular basis of the cardiotoxicity of anthracyclines remains a matter of debate. The cardiotoxicity

of the drug appears to be distinct from its therapeutic mechanism, and has been attributed to a large number of effects, including apoptosis (*Figure 1*), alterations in iron homeostasis, deregulation of calcium homeostasis both in the sarcoplasmic reticulum and in the mitochondria, and mitochondrial dysfunction. However, the common trigger of these events appears to be linked to an oxidative stress caused by the production of reactive oxygen species (ROS).

Generation of ROS by anthracyclines

The chemical structure of anthracyclines consists of a tetracycline moiety containing a quinone and a con-

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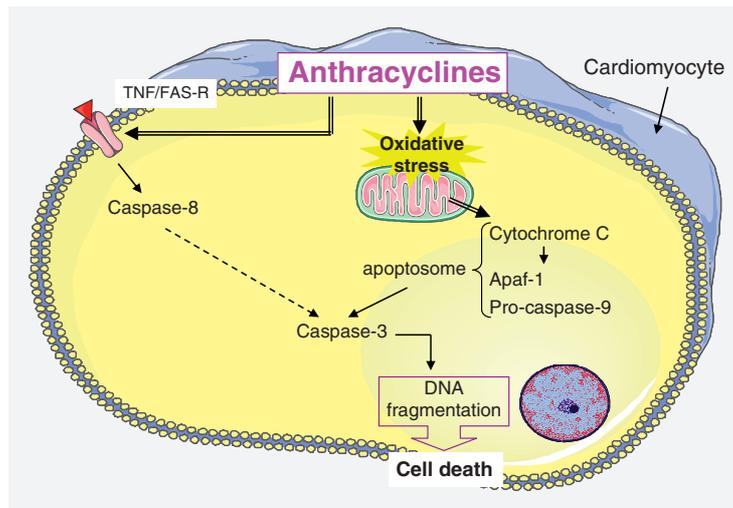


Figure 1. Apoptosis hypothesis for the cardiotoxicity of anthracyclines. Apaf-1, ?; TNF/FAS-R, tumor necrosis factor/ fatty acid synthase receptor. AQ1

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jugated amino sugar residue (Figure 2). In the cellular environment, anthracyclines might undergo redox activation through their interaction with several flavoprotein oxidoreductases (Figure 3). This semiquinone can rapidly auto-oxidize using molecular oxygen (O_2) as an electron acceptor, returning to the parent compound which is then available for a new redox cycle. This reaction leads to the formation of superoxide anion ($O_2^{\bullet-}$), which, in aerobic

conditions, can be produced in substantial amounts. Driven by superoxide dismutases (SOD), or spontaneously in acidic pH, superoxide anion is converted into hydrogen peroxide (H_2O_2) which, in the presence of traces of transition metals such as iron or copper, will be converted to the very reactive oxidizing species, hydroxyl radical (HO^{\bullet}).

These mechanisms are compounded by the fact that anthracyclines can directly form complexes

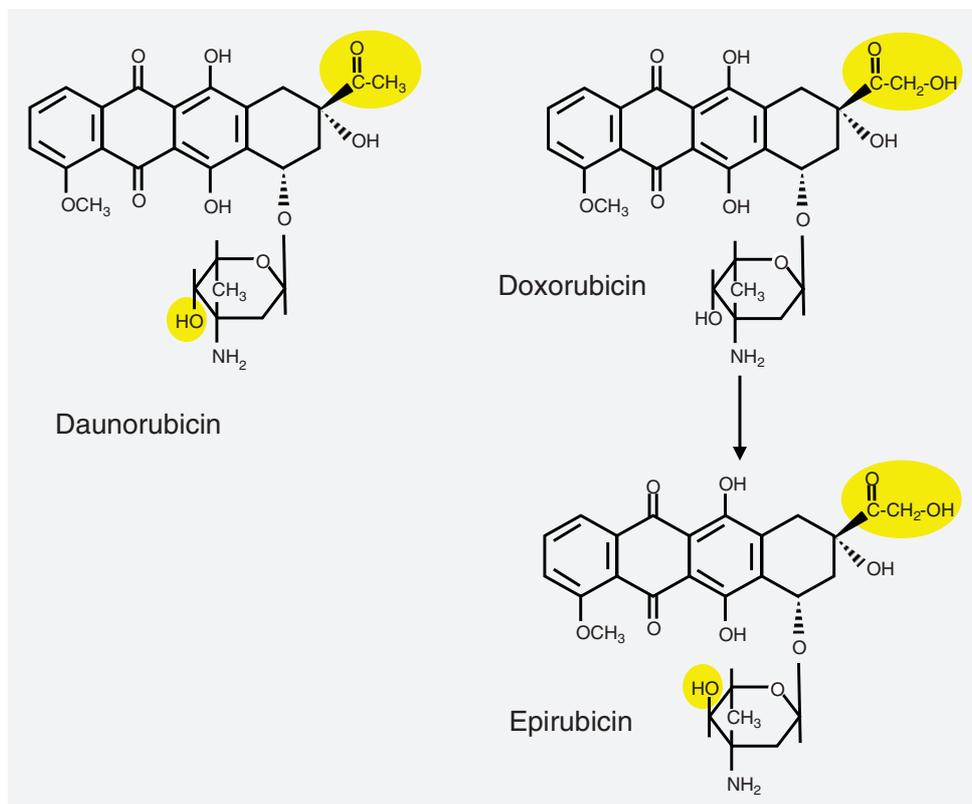


Figure 2. Molecular structures of anthracyclines.

Protection against the cardiotoxicity of anthracyclines in experimental models

Despite some conflicting evidence, possibly attributable to variability in the delivery of antioxidants to the site of generation of ROS, support for ROS-driven oxidative damage to cardiac cells comes from studies using antioxidant treatment that has conferred protection from cardiotoxicity. For instance, vitamin E [3,4], lycopene [5], sulfur-containing antioxidants (glutathione [6,7], mercaptopropionyl glycine [8], *N*-acetyl cysteine [4]), and also antioxidant enzymes such as SOD [9,10] or catalase [9] have been shown to protect against the cardiotoxicity of anthracyclines in several experimental models (Table I). Moreover, evidence for this theory concerning ROS as the primary initiator of anthracycline cardiotoxicity has been obtained in several studies on transgenic animals overexpressing antioxidant enzymes [11–14], which are largely protected from myocardial damage during treatment with anthracycline (Table II).

As the interaction of anthracyclines with iron is considered to be of importance in exerting their deleterious effects on the heart, some transition metal chelators have been tested, with success [15]. For instance, dexrazoxane (ICRF-187), a prodrug from an ethylenediamine tetra-acetic acid analog that acts via displacing irons from anthracycline–iron complexes and removing free irons from the vicinity of biomolecules, has been proposed for clinical use as a cardioprotector and found to be successful [16].

Several other strategies have also been developed [17] in order to reduce the cardiotoxic effects associated with anthracyclines.

Clinical data

Clinical features of anthracycline cardiotoxicity

The damage to the heart that occurs after anthracycline therapy can be categorized as:

- Early cardiotoxicity: happening during anthracycline treatment or in the first year after its completion, which manifests as non specific ST-segment and T-wave abnormalities.
- Late cardiotoxicity: happening at least 1 year after the completion of anthracycline treatment, which is cumulative, dose-related and can result in congestive heart failure and left ventricular dysfunction.

It has been reported that more than 50% of patients exposed to anthracyclines show cardiac abnormalities 10–20 years after the initial oncological diagnosis: arrhythmias were found to occur in 40% of patients, whereas 5% developed congestive heart failure [18].

There is a wide variation in the frequency of both clinical and subclinical cardiotoxicity after anthracycline therapy. In children, studies have shown that the prevalence of subclinical cardiac damage was more than 57% at a median of 6.4 years after treatment, and that the incidence of clinical heart failure was 16% 0.9–4.8 years after the treatment. In adults, the prevalence of subclinical cardiac damage has been reported to be 36% during anthracycline therapy, and the incidence of clinical heart failure 30% at a median of 37 months after the treatment [19].

The cardiac side effects of anthracyclines also depend on the schedule of its administration: continuous infusion over 24–92 h rather than rapid intravenous injection could reduce the cardiotoxicity of these agents [18].

Early detection and treatment of cardiotoxicity can significantly reduce the development of clinical manifestations. While the evolution of diastolic function assessed with echocardiography is an early sign of anthracycline-induced cardiac dysfunction, several studies have confirmed the usefulness of measuring B-type natriuretic peptide, which is increased before the development of left ventricular dysfunction, in the diagnosis of congestive heart failure.

Strategies to reduce the cardiotoxicity of anthracyclines

Figure 4 summarized the factors involved in the toxicity of anthracyclines and some strategies that are available to reduce the toxicity. We [20] and others [21] have reported on these aspects in greater depth elsewhere.

From a clinical point of view, the prevention of anthracycline cardiotoxicity relies on three approaches: rigorous cardiac monitoring, the use of anthracycline analogs with lower cardiotoxicity, and modifications of the program of administration. The use of cardioprotective agents during chemotherapy would be of great interest in achieving optimal use of anthracyclines, but the major concern is whether a cardioprotective agent could provide a selective decrease in the incidence and intensity of heart damage without reducing the antitumor efficacy of the chemotherapy and without negative side effects.

Anthracycline toxicity can be minimized by:

- Changing the process of administration to one of continuous infusion.
- Reducing the total cumulative dose to <400 mg/m².
- Using liposome-encapsulated anthracyclines.
- Reducing the amount of free iron by the use of dexrazoxane (however, this compound is not recommended at the beginning of treatment, because of the possibility that it could diminish the effect of anticancer agents [16,22]).

Table 1. Experimental studies showing the use of antioxidants in the prevention of the cardiotoxic effects of doxorubicin (Dox) or epirubicin (Epi).

Antioxidant	Model	Dose	Results	Ref.
Vitamin E	Rat	High doses	Abolition of ST-segment elevation induced by the administration of a single dose of Dox, reduction of cardiac enzymes (CPK-MB, LDH).	[3]
Vitamin E <i>N</i> -acetyl cysteine	Rat	100 mg/kg per day for 10 days 100 mg/kg	Protection towards lipid tissue cardiac and hepatic peroxidation induced by the administration of a single dose of Dox (20 mg/kg; i.p.). Protection of action potentials and cardiac electric activity.	[4]
<i>N</i> -(2-mercapto-propionyl) glycine)	Rat	2.5 mg/kg by mouth	Reduction of lipid tissue cardiac peroxidation (TBARS) and of cardiac enzymes release (CPK-MB, LDH), induced by the administration of a single dose of Dox (15 mg/kg; i.p.).	[8]
Lycopene	Rat	4 mg/kg per day for 10 days by mouth	Protection towards tissue cardiac and renal oxidation induced by the administration of a single dose of Dox (10 mg/kg). Reduction of cardiac and renal histological alterations.	[5]
Glutathione	Rat	5 mg/kg	Reduction of cardiac tissue lipid peroxidation (MDA) and of cardiac enzymes release (CPK-MB, LDH), induced by the administration of a single dose of Dox (20 mg/kg). Reduction of cardiac histological alterations.	[6]
	Rat	250–500 mg/kg iv	Reduction of QT elongation and of cardiac contractility alterations, induced by the administration of repeated doses of Dox (3 mg/kg/week, 4 weeks, i.v.). Reduction of cardiac histological alterations.	[7]
SOD Catalase	Rat Adult cardio-myocytes	10IU/ml 10IU/ml	Prevention of Dox (10 μ M) or Epi (10 μ M)–induced reduction of cardio-myocytes' contractility.	[9]
Mn TBAP (SOD mimic)	Rat Adult cardio-myocytes		Prevention of Dox (1–40 μ M)–induced release of LDH and formation of antioxidants. Protection of aconitase activity.	[10]

CPK-MB, creatine phosphokinase-MB; LDH, lactate dehydrogenase; MDA, ???; Mn TBAP, manganese ???; SOD, superoxide dismutase; TBARS, ????

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Table II. Studies in transgenic animals that overexpress antioxidant enzymes and are protected from anthracycline-induced myocardial damage.

Enzyme over-expressed	Model	Results	Ref.
GPx1	Mice B6C3	Better resistance to the acute effects of in-vitro administration of 5 $\mu\text{mol/L}$ Dox (contractility, EDLVP, heart rate). Preservation of mitochondrial function	[13]
Mn SOD	Mice B6C3 \pm KO iNOS	Protection against mitochondrial damage induced by Dox (20 mg/kg)	[11]
Human Mn SOD	Mice B6C3	Protection against Dox-induced ultrastructural alterations and mitochondrial lesions Reduction in serum concentrations of creatine kinase and LDH	[14]
Catalase Cardiac promoter	Mice	Protection against cardiac damage (lipid peroxidation), increase in serum creatine phosphokinase, and isolated atrial functional alterations induced by Dox (20 mg/kg)	[12]

Dox, doxorubicin; EDLVP, end-diastolic left ventricular pressure; GPx1, ?; iNOS, knockout inducible nitric oxide synthase; LDH, lactate dehydrogenase; Mn SOD, manganese superoxide dismutase.

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- Lessening the production of ROS with *N*-acetyl cysteine, coenzyme Q10, or a combination of antioxidant vitamins. Other cardioprotective agents such as L-carnitine, probucol, and deferoxamine are being investigated [23].

Finally, an appropriate treatment of early and late cardiac events is necessary, to slow down the evolution of anthracycline-induced cardiotoxicity. Early dysfunction such as arrhythmias and pericarditis is treated with antiarrhythmic agents [24] and aspirin. For late dysfunction, angiotensin-converting enzyme inhibitors [25] and β -blockers form the basis of treatment. Angiotensin-converting enzyme inhibitors have been shown to slow the progression of left ventricular dysfunction in several clinical settings and, in patients undergoing high-dose chemotherapy, early treatment with enalapril seemed to prevent the development of late cardiotoxicity and the occurrence of adverse clinical events [25].

Conclusion

The molecular mechanisms explaining the cardiac toxicity of anthracyclines are complex, but it appears that the induction of an oxidative stress within myocardial tissue constitutes a common denominator. Some promising new strategies to reduce the production of ROS and protect heart function are now available to patients and can lessen the myocardial injury that is associated with the use of anthracyclines. ■

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