Research Article **ISSN 2639-944X**

Journal of Medical - Clinical Research & Reviews

Anthracycline Cardiotoxicity: From Mechanisms to Prevention Strategies

Amelia Morgillo[1*], Marcello Mazzarella[3], Maria Francesca Randazzo[3], Naomi Mancino[1], Marialessia Talessi[1] and Edoardo Marovino[4]

[1]*Department of Medicine and Surgery – University of Siena.*

[2]*Department of Medicine and Surgery – Saint Camillus International Medical University of Health Science – Rome.*

[3]*Department of Medicine and Surgery – University of Torino.*

[4]*Department of drug sciences and department of biology and biotechnology "L. Spallanzani"-, University of Pavia.*

[*]Correspondence:
Amelia Morgillo, Department of Medicine and Surgery – University of Siena, Via Innico Caracciolo 12, Airola(bn) 82011

Received: 29 Dec 2022; **Accepted:** 26 Jan 2023; **Published:** 30 Jan 2023

Citation: Morgillo A, MazzarellaM, Randazzo MF, et al. Anthracycline Cardiotoxicity: From Mechanisms to Prevention Strategies. J Med - Clin Res & Rev. 2023; 7(1): 1-5.

ABSTRACT

Introduction: *Anthracyclines are among the most powerful antineoplastic drugs ever developed and, even today, they are widely used according to various association schemes in the onco-hematological field. However, cardiotoxicity remains one of the most feared and characteristic side effects, both short and long term, often causing the premature interruption of therapy or irreversible effects after their suspension. In this article, we want to explain the underlying biological mechanisms, the clinical presentation characteristics and the possible strategies to prevent it.*

Materials and Methods: *A computerized research was carried out for the articles to be inserted through use of international databases PUBMED, RESEARCHGATE and GOOGLE SCHOLAR, by typing in keywords such as "anthracyclines cardiotoxicity" and "cardioprotection strategies for anthracycline toxicity" and related articles.*

Discussion and Conclusions: *The toxicity of these drugs on the heart represents the limiting factor both for their indications and for the success of the therapy, sometimes being the cause of premature interruption or impossibility of use in some patients. It depends especially on the cumulative dose used in the single patient and on the pre-existing risk conditions for the development of these ADRs, both in the short and long term. However, there are strategies that can avoid or reduce the damage, both related to the formulation of the compounds and to the co-administration of other drugs.*

Keywords
Anthracyclines, Cardiotoxicity, Chemotherapy, Pharmaco-vigilance.

Introduction
Anthracyclines are a class of antibiotics initially isolated from "Streptomyces peucetius" that include compounds like daunorubicin, doxorubicin, idarubicin and epirubicin. They are actually used in oncology for the treatment of a wide variety of cancers such as breast, endometrial, genital and lung cancers and in the treatment of some sarcomas, while the main hematological application of daunorubicin is acute leukemia [1,2]. Chemically, they are hydrophobic planar molecules, with a quinonic structure that improves the catalysis of redox reactions, promoting the generation of oxygen free radicals at the base of the anticancer effects, as well as many of the collateral effects. In particular, the two most used molecules in clinical practice are doxorubicin and daunorubicin Figure 1 [3]. From a structural point of view, they have in common an aglyconic portion and a carbohydrate portion. The aglycone is a condensed 4-ring structure that has a quinone on the C ring adjacent to a hydroquinone on the B ring. It also contains a methoxyl group on the C-4, in the D ring, and a small chain at the C-9 containing a carbonyl group [4]. The only difference between the two molecules is that the side chain in C-9 ends first with a primary alcohol hydroxyl group -CH2OH while the other ends with a simple methyl [5].

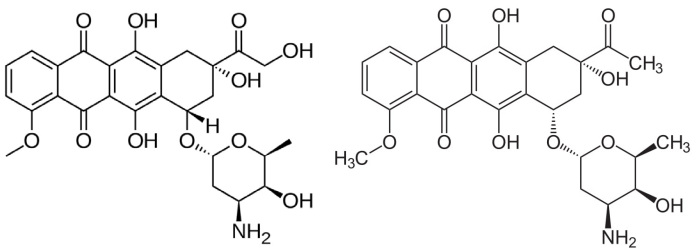

Figure 1: Chemical structure of doxorubicin (A) and daunorubicin (B).

This small difference from a structural point of view has important repercussions on the spectrum of action in addition, the potency of the two drugs [6]. The carbonyl group at position 14 of the anthracene ring is important from both a pharmacodynamic and a toxicological point of view [7]. In fact, when this is metabolized to a secondary alcoholic group by some cytosolic reductases, the activity of the drug decreases significantly; on the other hand, the formation of secondary alcohol derivatives is at the basis of toxicity [8]. The mechanisms of action are different and associate the antiproliferative effect with the ability of these molecules to:

- generate oxygen free radicals, resulting in DNA damage and lipid peroxidation
- intercalate in DNA, forming ternary complexes with Topoisomerase II which induce double-stranded breaks in the DNA molecule and induce apoptosis of the cell
- induce histone expulsion, compromising the DNA repair mechanisms

Unfortunately, among the side effects of anthracyclines, the best known is their ability to cause damage to the myocardium of varying severity and course, often depending on the dose and premorbid status [9]. In this article we will describe in detail the mechanisms of cardiac toxicity and some related cardioprotection techniques.

Materials and Methods

Computerized research was carried out for the articles to be inserted through use of international databases PUBMED, RESEARCHGATE and GOOGLE SCHOLAR, by typing in keywords such as "anthracyclines cardiotoxicity" and "cardioprotection strategies for anthracycline toxicity" and related articles. We also have consulted the package leaflet of the medicinal products doxo and daunorubicin together with some paper books of toxicology applied to drugs to complete the description.

Discussion

Anthracyclines are the class of antineoplastic drugs most closely associated with cardiotoxicity. "Chemotherapy cardiotoxicity" refers to the harmful effects involving the heart following chemotherapy treatment, due to direct effects of the drug or indirect effects (thrombogenic states or alterations in the haemodynamic flow) [10]. The Cardiac Review and Evaluation Committee definition specifically defines chemotherapy cardiotoxicity in the presence of one or more of the following:

- Decrease in LVEF (left ventricular ejection fraction) overall or affecting mainly the interventricular septum.
- Signs or symptoms of heart failure.
- Reduction in LVEF of at least 5% to <55%, in the presence of signs or symptoms of heart failure.
- 10% reduction in LVEF to <55% in asymptomatic patients.

Another classification (proposed by Suter and Ewer) was made between drugs, which, such as anthracyclines, induce irreversible heart damage, called Type I, and others that more often induce reversible cardiac dysfunction, called Type II [11]. While Type I toxicity correlates with cell loss, Type II drugs induce cardiomyocyte dysfunction predominantly through mitochondrial alterations. In the context of the cardiotoxicity of anthracyclines, we can distinguish three forms of presentation:

- Acute, rather rare and generally benign; in less than 1% of patients, during or a few hours after the anthracycline infusion, presenting with arrhythmias, changes in the ECG or with an acute and transient reduction in myocardial contractility. Its incidence can be significantly reduced by slowing the infusion rate [12].
- Early, within one year of treatment, representing the most frequent form. (98% of cases of cardiotoxicity were found to be of this type) [13].
- late, more than a year after therapy, often 5-10 years, and manifests itself as progressive congestive heart failure and often refractory to treatment, with high mortality [14]

Various risk factors (Figure 2) have been identified for the development of anthracycline cardiotoxicity and numerous scores have been developed to estimate in advance the risk of onset of cardiotoxicity; however none of these has been validated prospectively, therefore the risk estimate remains to date mostly linked to the clinical judgment of the oncology team [15].

Risk factor	Increased risk
Age	Younger
Gender	Female
Method of administration	Rapid intravenous injection
Cumulative dose	Exceeding: Daunorubicin 550–800 mg/m^2 Doxorubicin 400–550 mg/m^2 Epirubicin 900–1000 mg/m^2 Idarubicin 150–225 mg/m^2 Amsacrine 580 mg/m^2 Mitoxantrone >100–140 mg/m^2
Mediastinal radiation	Early mediastinal radiation, or concomitant doxorubicin exceeding a cumulative dose of 450 mg/m^2
Previous cardiovascular disease	Hypertension, coronary disease

Figure 2: Risk factors for the development of cardiotoxicity.

Among the risk factors, however, the most important remains the cumulative dose administered, with different thresholds depending on the type of anthracycline: for doxorubicin, it seems that cumulative doses <300 mg / m^2 are safe, while the incidence of heart failure increases at 7-25% for doses of 550 mg/m^2 [16]. The maximum cumulative recommended lifetime doses are 400-550 mg / m2 in adults with a standard infusion rate, slightly higher when administered slowly. Epirubicin has a lower relative cardiotoxicity than doxorubicin, and can be administered up to a maximum recommended cumulative dose of 900 mg / m^2 [17]. Greater tolerability has also been observed with liposomal formulations, for which doses of 20-50 mg / m^2 every 4 weeks are currently recommended. Anthracyclines can directly damage DNA due to the generation of reactive oxygen species (ROS), leading to oxidized nucleotides, base mismatches, point mutations and single-strand DNA breaks [18]. ROS production also causes DNA damage-independent stimulation of cytotoxic mechanisms, resulting from oxidative modifications of the protein, particularly lipid peroxidation [19]. Finally, anthracyclines interfere with DNA helicase activity and DNA strand separation. A hallmark of chronic anthracycline-induced cardiotoxicity is the reduction in left ventricular wall thickness due to cardiomyocyte loss. Anthracycline-induced apoptosis is probably mediated by pathways related to caspase 3, activated by p53 and / or TNF signaling. Mechanisms suggested for the development of cardiomyopathy include accumulation of toxic metabolites (eg doxorubinicol), autophagy, peroxynitrite and ROS production, TOP2B inhibition, and disruption of mitochondrial homeostasis / integrity [20]. Anthracyclines could cause such ROS generation because they are reductively activated to a semiquinone radical, which undergoes a redox cycle, thus producing superoxide (O2-) and hydrogen peroxide (H_2O_2) [21]. In the presence of iron, anthracyclines can form complexes of Fe 3+ -anthracyclines, which further catalyze the conversion of H_2O_2 into various ROS species, including cytotoxic hydroxyl radicals (OH -; Fenton reaction). The Redox cycle from a single anthracycline molecule could lead to the accumulation of ROS. This so-called "ROS and iron" hypothesis is very popular for explaining the cardiotoxicity of anthracyclines, but the postulated relevance for chronic cardiotoxicity lacks convincing experimental evidence [22].

Various strategies have been made over the years to prevent cardiotoxicity from this compound [23]. An estimate of the risk of cardiotoxicity, including a thorough medical history and physical examination measurement of cardiac biomarkers estimate of left ventricular function. Above all, the lines of research have developed two main directions:

- pharmacological cardioprotection (Figure 3), where most of the data comes from small studies and early follow-up, and it is therefore difficult to identify a single most effective agent among those listed. Nonetheless, based on the accumulated evidence it can be concluded that prophylactic cardioprotective treatment is strongly recommended in patients at high risk of developing cardiotoxicity, and should also be considered in patients at low risk when receiving high dose anthracycline-containing chemotherapy treatments [24]. Considering that at least in part the cardiotoxicity of anthracyclines is correlated to the generation of free radicals, an attempt was made to prevent this effect by acting on the redox response and reducing oxidative stress. Dexrazoxane is a metal chelator tested as a cardioprotective agent in patients with anthracycline-treated breast cancer. In two randomized trials the drug showed a promising protective effect

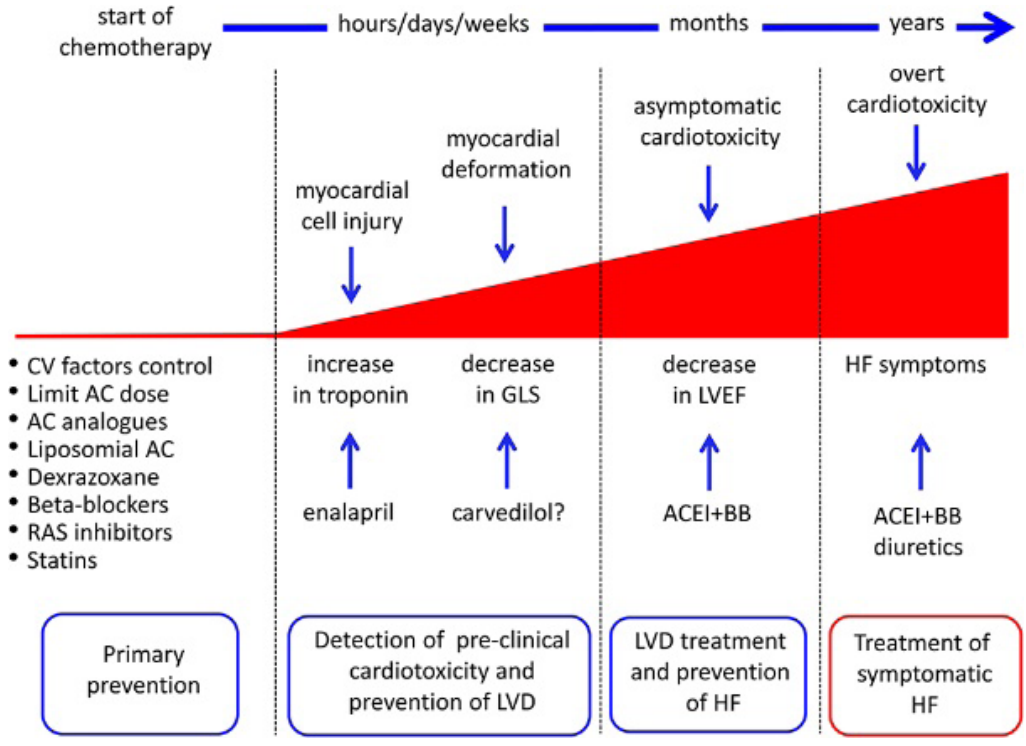

Figure 3: Cardioprotection mechanisms proposed for anthracycline cardiotoxicity.

when compared to placebo, leading to its approval by the FDA in 1995 [25]. Nevertheless, the risk of a potential interference with the therapeutic action of anthracyclines (due to its inhibitory action Topoisomerase has led to its limited use. In Europe, dexrazoxane is only approved for use in adults with advanced breast cancer receiving anthracycline chemotherapy beyond certain cumulative doses. The limitation to adulthood stems from controversies related to a possible increase in the risk of second malignancies; however, a recent analysis of the literature has not confirmed this risk. More recently, the cardioprotective potential of drugs already used in cardiology for other purposes, such as ACE inhibitors, sartans and β-blockers; these drugs have the advantage of a reduced cost statins, finally, are another class of drugs that have shown promise for cardioprotection purposes; we currently only have data from observational studies, but randomized studies are ongoing [26].

The use of modified release liposomal formulations, where the drug is encapsulated within unilamellar vesicles of unsaturated phospholipids, allowing an increased concentration at the level of the tumor tissue, due to the increased capillary permeability observed at the level of the distorted microcirculation, on the other hand, limiting its accumulation in healthy tissues and in particular in the heart because liposomes, due to their size, with difficulty overcome the "tight junctions" of myocardiocytes [27]. Since the mid-1990s, a pegylated liposomal form of doxorubicin has been on the market, now used in the treatment of metastatic breast cancer, advanced ovarian cancer, AIDS-related Kaposi's sarcoma and refractory / relapsing multiple myeloma [28]. The coating by the hydrophilic polyethylene glycol (PEG) polymer promotes evasion from mononuclear phagocytes and produces a stabilization of the molecule, with reduced adhesion to cells, vascular endothelium and other surfaces. A non-pegylated liposomal form of doxorubicin entered the market in 2000, with the sole indication for the treatment of metastatic breast cancer, with an efficacy comparable to the previous one and a potential reduction in toxicity [29].

BIOMARKERS OF CARDIAC DAMAGE

In addition to instrumental tests such as electrocardiography and echocardiography and clinical data, many laboratory biomarkers that can be measured on blood have been proposed to evaluate patients at risk even at an early stage. Unfortunately, few are sensitive and specific to the myocardium, and some are difficult to dose. In addition to markers of acute injury such as cardiac troponins, myoglobin and creatine phosphokinase (CPK), molecules associated with long-term damage such as myocardial fibrosis and cardiac remodeling have been identified. Some, such as galectin-3 and sST2 (soluble interleukin 33 receptor protein) have demonstrated prognostic relevance and are extensively studied. In particular, the latter two seem to be possible prognostic biomarkers in patients with heart failure associated with the degree of fibrosis. We should not forget the atrial natriuretic peptide, considered in all guidelines as markers of acute and chronic heart failure and for the stratification of the risk of mortality and morbidity in all cardiovascular diseases.

Conclusions

Drug-induced cardiotoxicity is a significant problem as cancer patients are often long-surviving, today over 3 million in Italy, and often have to deal with even severe long-term post-cancer effects and cardiotoxicity is certainly among the most strongly limiting ones. Anthracyclines have a peculiar mechanism, are among the best known, but not unique, capable of causing such effects, and therefore deserve special attention [30].

References

1. Urbanová D, Mladosievicová B. Kardiotoxicita antracyklínovej liecby vo svetle nových biochemických diagnostických mozností Cardiotoxicity of antracycline treatment in the light of new biochemical diagnostic options. Vnitr Lek. 2007; 53: 669-677.
2. Fandeev OA, Vasechkin SS, Alekhin MN, et al. Clinical value of antracycline toxicity modern approaches to diagnosis prevention and treatment. Kardiologiia. 2011; 51: 40-46.
3. Malato A, Saccullo G, Fazio G, et al. Drug-related cardiotoxicity for the treatment of haematological malignancies in elderly. Curr Pharm Des. 2010; 16: 2872-2879.
4. Pop RM, Bocsan IC, Buzoianu AD, et al. Evaluation of the Antioxidant Activity of Nigella sativa L and Allium ursinum Extracts in a Cellular Model of Doxorubicin-Induced Cardiotoxicity. Molecules. 2020; 25: 5259.
5. Elitok A, Oz F, Cizgici AY, et al. Effect of carvedilol on silent anthracycline-induced cardiotoxicity assessed by strain imaging A prospective randomized controlled study with six-month follow-up. Cardiol J. 2014; 21: 509-515.
6. Kaya MG, Ozkan M, Gunebakmaz O, et al. Protective effects of nebivolol against anthracycline-induced cardiomyopathy a randomized control study. Int J Cardiol. 2013; 1: 2306-2310.
7. Minichillo S, Pantaleo MA, Nannini M, et al. Efficacy of weekly docetaxel in locally advanced cardiac angiosarcoma. BMC Res Notes. 2015; 8: 325.
8. Gergely S, Hegedűs C, Lakatos P, et al. High Throughput Screening Identifies a Novel Compound Protecting Cardiomyocytes from Doxorubicin-Induced Damage. Oxid Med Cell Longev. 2015; 2015: 178513.
9. Collins Y, Lele S. Long-term pegylated liposomal doxorubicin use in recurrent ovarian carcinoma. J Natl Med Assoc. 2005; 97: 1414-1416.
10. Bhagat A, Kleinerman ES. Anthracycline-Induced Cardiotoxicity: Causes, Mechanisms and Prevention. Adv Exp Med Biol. 2020; 1257: 181-192.
11. McGowan JV, Chung R, Maulik A, et al. Anthracycline Chemotherapy and Cardiotoxicity. Cardiovasc Drugs Ther. 2017; 1: 63-75.
12. Armenian S, Bhatia S. Predicting and Preventing Anthracycline-Related Cardiotoxicity. Am Soc Clin Oncol Educ Book. 2018; 38: 3-12.
13. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015; 131: 1981-1988.
14. Nicolazzi MA, Carnicelli A, Fuorlo M, et al. Anthracycline and trastuzumab-induced cardiotoxicity in breast cancer. Eur Rev Med Pharmacol Sci. 2018; 22: 2175-2185.
15. Narezkina A, Nasim K. Anthracycline Cardiotoxicity. Circ Heart Fail. 2019; 12: e005910.

16. Saleh Y, Abdelkarim O, Herzallah K, et al. Anthracycline-induced cardiotoxicity: mechanisms of action, incidence, risk factors, prevention and treatment. Heart Fail Rev. 2021; 26: 1159-1173.
17. Sawicki KT, Sala V, Prever L, et al. Preventing and Treating Anthracycline Cardiotoxicity: New Insights. Annu Rev Pharmacol Toxicol. 2021; 6: 309-332.
18. Russo M, Della Sala A, Tocchetti CG, et al. Metabolic Aspects of Anthracycline Cardiotoxicity. Curr Treat Options Oncol. 2021; 22: 18.
19. Tantawy M, Pamittan FG, Singh S, et al. Epigenetic Changes Associated With Anthracycline-Induced Cardiotoxicity. Clin Transl Sci. 2021; 14: 36-46.
20. Sala V, Della Sala A, Hirsch E, et al. Signaling Pathways Underlying Anthracycline Cardiotoxicity. Antioxid Redox Signal. 2020; 32: 1098-1114.
21. Alvarez-Cardona J, Lenihan DJ. Anthracycline Cardiotoxicity: It Is Possible to Teach an Old Dog Some New Tricks. Cardiol Clin. 2019; 37: 355-363.
22. Varghese SS, Eekhoudt CR, Jassal DS. Mechanisms of anthracycline-mediated cardiotoxicity and preventative strategies in women with breast cancer. Mol Cell Biochem. 2021; 476: 3099-3109.
23. Songbo M, Lang H, Xinyong C, et al. Oxidative stress injury in doxorubicin-induced cardiotoxicity. Toxicol Lett. 2019; 307: 41-48.
24. Nishi M, Wang PY, Hwang PM. Cardiotoxicity of Cancer Treatments: Focus on Anthracycline Cardiomyopathy. Arterioscler Thromb Vasc Biol. 2021; 41: 2648-2660.
25. Özdoğru İ. Anthracycline-induced cardiotoxicity. Turk Kardiyol Dern Ars. 2014; 42: 274-276.
26. Russo M, Bono E, Ghigo A. The Interplay Between Autophagy and Senescence in Anthracycline Cardiotoxicity. Curr Heart Fail Rep. 2021; 18: 180-190.
27. Cruz M, Duarte-Rodrigues J, Campelo M. Cardiotoxicity in anthracycline therapy: Prevention strategies. Rev Port Cardiol. 2016; 35: 359-371.
28. Verberne HJ, Verschure DO. Anthracycline-induced cardiotoxicity: Is there a role for myocardial ^{123}I-mIBG scintigraphy. J Nucl Cardiol. 2020; 27: 940-942.
29. Mele D, Tocchetti CG, Pagliaro P, et al. Pathophysiology of anthracycline cardiotoxicity. J Cardiovasc Med Hagerstown. 2016; 1: S3-S11.
30. Chaudry M, Banchs J, Chavez-MacGregor M. Anthracycline or trastuzumab-related cardiotoxicity: do we have a predictive biomarker. Biomark Med. 2016; 10: 315-328.