Update on pathophysiology and preventive strategies of anthracycline-induced cardiotoxicity

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Abstract: Anthracycline chemotherapy has a prominent role in treating many forms of cancer. Unfortunately, cardiotoxic side effects represent a serious limitation to their use, with doxorubicin being the leading drug of the group. Indeed, anthracyclines-induced cardiomyopathy is an important public health concern because it may not be detected for many years and remains in a life-long treat. Even after decades of investigation, neither the exact mode of action of anthracyclines nor the pathways leading to their side effect are fully understood. It is increasingly important to establish collaboration between oncologists and cardiologists to improve the management of cancer patient receiving anthracyclines. This article reviews the clinical course, pathogenesis, cardiac monitoring and new concepts in diagnosing and preventing anthracyclines-induced cardiotoxicity.

Keywords: Anthracycline; Cancer; Cardio-protection; Cardiotoxicity; Chemotherapy; Doxorubicin

1. Introduction

Cancer is the second leading cause of death after cardiovascular diseases in the USA. An estimated 14.5 million people are currently living with a history of cancer and this number is anticipated to rise to 19 million over the next 10 years.(1) Recently, cancer outcomes significantly improved due to earlier detection and novel targeted therapies, with anthracycline chemotherapy playing a key role in the modern era of cancer therapy.(2) Unfortunately, anthracycline treatment is compromised by an insidious cardiomyopathy and heart failure (HF). The anthracycline anti-tumour and cardiotoxic mechanisms have not been fully elucidated and continue to evoke extensive interest in basic science and clinical research.(3-6) This review summarizes the potential cardiovascular toxicities of anthracyclines and their mechanistic pathways. We also review the clinical course, cardiac monitoring and new concepts in diagnosing and preventing anthracyclines cardiotoxicity.

2. Anthracyclines

Anthracyclines, discovered a half century ago, are listed among the World Health Organization (WHO) model list of essential medicines.(7) Daunorubicin (DAU) and doxorubicin (DOX) (Figure 1) were the first to be used in clinical practice, although other drugs have been developed within this family, like epirubicin (EPI), and idarubicin.(3) The structure is formed of an anthraquinone chromophore bound to an aminoglycoside.(8, 9) In the early 1960s their chemical characterization experienced a substantial increase after anticancer therapeutic activity was described. They rank among the most effective and frequently used antineoplastic agents and remain indispensable components of modern chemotherapy protocols effective against a broad spectrum of solid tumours and leukaemia.(10-12)

3. Anticancer mechanism of anthracyclines

Fifty years on from its discovery, anthracycline anti-tumour and cardiotoxic mechanisms alike remain to evoke considerable interest in basic science research.(11) The exact mechanism of anthracycline-induced cardiotoxicity remains unclear; however, several pathways have been proposed (Figure 2).(12-14)

3.1. Topoisomerase II poisoning

The principal molecular target for anthracyclines antitumour action is topoisomerase 2 (TOP2) in the proliferative cancer cells. TOP2 is an adenosine triphosphate (ATP)-dependent enzyme, which is expressed as isoenzymes TOP2α and TOP2β in humans. TOP2α is the most prevalent and is highly expressed in proliferating cells. Anthracyclines inhibit TOP2 upon formation of a ternary complex, consisting of double-stranded DNA, TOP2 and the anthracycline (DNA-TOP2-DOX). The stabilization of the cleavage complex impedes DNA resealing, resulting in double-stranded DNA breaks. When bound to TOP2α, the complex inhibits DNA replication and induces apoptosis as intended in proliferating malignant cells.(5, 7, 10, 11, 13, 15-18) Damage to non-proliferating, quiescent cells, like the heart muscle, where TOP2β is the major form, results in heart muscle failure as a side effect.(18)

3.2. Intercalation

After cellular uptake, DOX localizes primarily in the nucleus and binds to DNA by intercalation, inhibiting both ribonucleic acid (RNA) transcription and DNA replication. DOX prefers to insert it planar chromophore into intercalation site containing adjacent guanine-cytosine (GC) base pairs, probably due to specific hydrogen-bond formation between DOX and guanine.(12, 13, 19) Activation of DNA damage responses induces cell death independent of TOP2.(12, 13)

3.3. Oxidative stress

DOX-induced release of free radicals, due to its metabolism, may cause oxidative stress, resulting in DNA damage and cell death (Figure 3).(3, 13, 14) The quinone structure permits DOX to act as electron acceptors in reactions mediated by oxoreductive enzymes. Via one-electron reduction, most notably, cytochrome P450 reductase, the anthraquinone structure forms a semiquinone radical.(12, 14) Other enzymatic systems are also known to activate DOX as well, including xanthine oxidase and nitric oxide synthase. Semiquinone radicals may induce free-radical injury to DNA of themselves, as well after interaction with molecular oxygen to generate superoxides, hydroxyl radicals and peroxides, causing DNA damage. The transfer of its unpaired electron will lead to the original quinone form.(3, 9, 12-14)

4. Antineoplastic agents and cardiomyopathy

Success in treating cancer might be followed by defeat from life-threatening conditions caused by cytotoxicity.(20) The most frequent type of cardiotoxicity in cancer treatment is anthracycline-related cardiomyopathy.(21) According to Lefrak et al., repeated administration of anthracyclines can result in permanent cellular and interstitial damage,(22) but new therapeutic agents such as trastuzumab, while they can also cause cardiomyopathy, induce transient and reversible myocyte dysfunction, resulting in better prognosis.(23, 24) Antineoplastic drugs are classified into type 1 and 2, depending on the chemotherapy-induced toxicity. Anthracyclines belong to Type I agents and cause irreversible and dose-dependent damage, which consist of cellular death, either via necrosis or apoptosis. Type II is caused by cellular dysfunction and is usually described as reversible, since no structural changes have been detected by myocardial biopsies of patients, and generally is not dose-related.(3, 20, 25, 26) Additional cardiovascular toxicity of several antineoplastic agents includes myocardial ischemia, arrhythmias, systemic hypertension and thromboembolic events.(20, 25)

5. Doxorubicin-induced cardiotoxicity

Although anthracyclines have been proven as useful antineoplastics, life-threatening cardiotoxicity as a side effect has been a limiting factor to their use.(10) It has long been considered that DOX exerts its anticancer and cardiotoxic action by distinct mechanisms: while the anticancer response was associated with DNA intercalation, TOP2 inhibition and apoptosis, the cardiotoxicity was mainly ascribed to oxidative stress. At present, it appears that such separation is not fully justified. It seems that beneficial (anticancer) and detrimental (cardiotoxic) responses to DOX are to some extent overlapping(27, 28). Despite over many years of research, the mechanisms have not been fully clarified.(4, 5)

5.1. Definition Cardiotoxicity

Cardiotoxicity is described by the National Cancer Institute in general terms as the 'toxicity that affects the heart' (www.cancer.gov/dictionary/).(29) However, historically, cardiotoxicity has been defined as a decrease in left ventricular ejection fraction (LVEF).(30) Unfortunately, there is not yet a consensus definition for cardiotoxicity that can be applied to all cancer types.(31)

5.2. Incidence and Risk factors

Anthracycline-related cardiotoxicity is broadly defined as acute onset (within the first week of therapy), early onset, and late onset (>1 year after therapy). Acute-onset toxicity, which occurs in less than 1 % of patients, is dose-independent. More common is late-onset toxicity, which manifests in a dose-dependent fashion, causing dilated cardiomyopathy that can occur decades from first exposure (25). A high cumulative anthracycline dose is a well-recognized risk factor for cardiac damage. The incidence of DOX cardiomyopathy is about 4% when the cumulative dose of DOX delivered is 500-550 mg/m^2, 18% when the dose is 551-600mg/m^2 and 36% when

the dose exceeds 600mg/m^2 albeit with substantial individual variation.(25, 26, 32) However, there is no completely safe dose and the cardiotoxic effects of any given dosage must be balanced with oncologic efficacy (33). Other risk factors include extremes of age (>65 or <4years), female gender, diabetes, prior mediastinal radiation therapy, hypertension, concomitant treatments and the presence of cardiac disease.(25, 27, 34) However, these factors represent continuous rather than dichotomous variables, which makes quantification of risk for any given patient challenging. One approach could be to stratify patients, allowing identification of patients at high risk who could receive more intensive clinical monitoring.(21) It is also important to know that some patient show a predisposition to develop HF, because of the many genetic modifiers that can accelerate the course of development of anthracycline cardiotoxicity.(35)

5.3. Cardiotoxic mechanisms

Many pathways, as shown in Figure 4 and explained below, are involved in the anthracycline-induced cardiotoxicity**.** Each of them may play a role in causing cardiotoxicity via different mechanism, by themselves or in cooperation with other pathways.(3)

5.3.1. Molecular mechanisms:

The molecular mechanisms of DOX induced cardiotoxicity include oxidative stress, accumulation of toxic metabolites, alterations in iron (Fe^{2+}) and calcium (Ca^{2+}) homeostasis, mitochondriopathy and interactions with TOP2ß.

Oxidative stress: DOX-induced release of reactive oxygen species (ROS)causes oxidative stress, resulting in DNA damage and cell death.

Toxic metabolites: A two-electron reduction, of the side chain carbonyl moiety converts anthracyclines to secondary alcohol, toxic metabolites at the myocardium level. The production of doxorubicinol in the case of DOX is up to 50 times more potent than the original compound at dysregulating $Ca^{2+}$and iron homeostasis.(3, 36)

Fe^{2+} and Ca^{2+} homeostasis: As shown earlier, formation of DOX-Fe^{2+} complexes may catalyse a Fenton reaction, Fe^{2+}-catalysed formation of hydrogen peroxide (H_2O_2) to hydroxyl radical (OH•), resulting in the generation of ROS. This proves that anthracyclines are capable of altering iron homeostasis and studies have indicated that iron loading aggravates the toxic effects of DOX.(3, 10, 34, 37) The major metabolic effects of anthracycline-induced mitochondrial toxicity are an increase in Ca^{2+} content and inhibition of ATP synthesis. The loss of mitochondrial Ca^{2+} loading capacity is due to the drug-induced malfunction of transporters involved in ion homeostasis.(37, 38)

Mitochondriopathy: Mitochondria is the most extensively injured subcellular organelle. DOX is retained in the mitochondrial inner membrane by forming a nearly irreversible complex with the mitochondrial phospholipid cardiolipin. Cardiolipin contains a high percentage of polyunsaturated fatty acids, making it particularly susceptible to peroxidative injury. Disrupting the association of inner mitochondrial membrane proteins with cardiolipin could enhance cytochrome C release into the cytosol in response to oxidant stress, activating caspase cascade and resulting in apoptosis.(34, 37)

Topoisomerase 2β: As said before TOP2ß is responsible for the damage to non-proliferating cells, like the heart muscle cells, as an adverse effect. Without TOP2ß, DOX cannot bind directly to DNA, protecting the cardiomyocytes against DNA double-strand breaks and transcriptome changes that are responsible for defective mitochondrial biogenesis and increased ROS accumulation. When bound to TOP2ß, mitochondrial dysfunction is triggered by the suppression of peroxisome proliferator-activated receptor (PPAR), which regulates oxidative metabolism, in adult mammalian cardiomyocytes.(7, 16, 18)

5.3.2. Histological pathophysiology

Repetitive induction of cardiomyocyte cell death without sufficient regenerative capacity is a plausible mechanism for DOX-induced cardiotoxicity. Indeed, when cumulative toxicity surpasses a threshold of reparable damage, a generic process of ventricular remodelling is triggered.(31) This remodelling includes alterations in cardiac gene expression leading to structural changes in the myocardial wall.(39) The main histological changes are shown in Table 1.

5.3.3. ErbB2/ERbB4 and NRG-1 signalling: cardiotoxicity of concomitant Trastuzumab and anthracyclines

Anthracycline therapy renders cardiomyocytes more susceptible to alterations in Neuregulin-1 (NRG-1), a member of the epidermal growth factor (EGF) family, and protein-tyrosine kinase (ErbB) pro-survival pathway.(7, 40) Trastuzumab (TRZ), a monoclonal antibody against the ErbB2 that is found to be overexpressed in 25% to 30% of breast cancer patients, is often used as adjuvant therapy in combination with DOX treatment.(41, 42) Zeglinski et al. proposed that the adjuvant use of TRZ could potentiate cardiomyocyte damage through a 'dual-hit' mechanism, which includes inhibition of NRG-1 survival signalling pathway and Angiotensin II (ANGII)-induced activation of NADPH oxidase, increasing the ability to further ROS production as shown in Figure 5.(20, 41) The potentiation of cardiac dysfunction of TRZ in conjunction with DOX could be due to the inherent ability of DOX to increase oxidative stress.(41) DOX administration produces a pool of vulnerable cardiomyocytes that are dependent on intact ErbB2-signalling for recovery, while TRZ blocks key receptors in the pathways that regulate cell survival.(20, 41)

6. Strategies for prevention

In Cardio-Oncology, the best treatment for chemotherapy-induced cardiotoxicity is prevention. A detailed history focusing on cardiovascular risk factors, pre-existing cardiovascular disorders and previous exposure to chemotherapy agents is mandatory. A comprehensive assessment of the benefits from treatment versus potential risks of cardiotoxicity should be performed.(43)

6.1. Primary prevention of cardiotoxicity from anthracyclines

Pharmacodynamic approaches can be applied for primary prevention of anthracycline-induced cardiotoxicity. Subsequently, the use of a cardioprotective agents in conjunction with the treatment is a possibility.(17) Besides that, it is also important to know that some patients show higher predisposition to develop HF and individual genotyping should be considered as a strategy for primary prevention in the future.(35)

6.1.1. Continuous infusion

Early in the 1980s, administering DOX by continuous infusion over forty-eight to ninety-six hours evidenced to be an effective mean to reduce the development of clinically evident chronic heart failure (CHF), while not diminishing tumour objective action.(44) Recently, Van Dalen et al. showed that an anthracycline infusion duration of six hours or longer diminish the occurrence of clinical HF and subclinical cardiac damage, while there was no significant difference in HF development using a peak dose of less than 60 mg/m^2 or 60mg/m^2 or more. (45) 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.(26, 35, 46) This strategy benefit is controversial in pediatric settings.(47)

6.1.2. Liposomal doxorubicin

Replacing conventional anthracyclines with liposomal formulations, which alters pharmacokinetics and tissue distribution without affecting antitumour efficacy, can reduce cardiotoxicity.(48) Due to their size, liposomes are too big to cross the gap junctions of normal endothelium in the heart and many other healthy tissues, but diffuse more readily through the leaky vasculature of tumours. 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 (PEG) embedded in the lipid layer; other formulations of DOX (Myocet®) adopt uncoated liposomes.(35, 49)

6.1.3. Less cardiotoxic analogues

Several adjustments of the anthracycline basic structure have been achieved to improve the pharmacological properties of the natural compound, with reduced cardiotoxicity.(48) Only few analogues have reached the stage of clinical approval; among them, EPI and idarubicin (IDA) are viable alternatives to DOX or DNR, respectively.(48) EPI is a semi-synthetic epimer of DOX, with an analogous oncological spectrum. Although the mechanism of action is similar to DOX, some of its physical, chemical and pharmacokinetic properties are different.(50) IDA, compared with DNR, has increased lipophilicity and cellular uptake and improved stabilization of a ternary drug-TOP2-DNA complex.(51) This drug may be administered orally(52) and there is some controversy about whether IDA offers advantages over DOX or DNR regarding cardiac toxicity.(53) Also, the analogues amrubicin and the novel anthracenedione (pixantrone) are prominently less cardiotoxic, but they are used in limited conditions.(54, 55)

6.1.4. Dexrazoxane

Given to the importance of oxidative stress, research has focused on drugs with antioxidant properties.(25, 26, 35) Exploratory clinical trials that probed the protective efficacy of high-dose vitamin E or N-acetylcysteine were uniformly disappointing. Dexrazoxane (DRZ), the only FDA-approved cardioprotective agent for anthracycline-induced cardiotoxicity, can chelate iron, before it converts O_2^- and H_2O_2 into more potent OH•.(56) It was previously thought to be the primary mechanism of cardioprotection however other antioxidants and iron-chelating agents, have been tested in animal models and in humans, but the protective effect of some is uncertain. Thus, iron chelation and mitigation of oxidative stress might not represent the only prevailing mechanism of cardioprotection. Indeed, DRZ precludes the formation of the ternary complex, DOX-DNA-TOP2ß, by forcing TOP2ß to assume a closed-clamp conformation (Figure 6). Therefore, cardiomyocyte damage or death will be prevented.(10, 18, 35) In clinical trials, DRZ has reduced the incidence of CHF and augmented LVEF.(34) Unfortunately, controversy surrounds its use due to possible compromise of antineoplastic efficacy and increase in secondary tumours, myelosuppression and infection.(17, 25) Due to the latter concerns its use in children was contraindicated by the European Medicines Agency (EMA) in 2011 and restricted to women with breast cancer who had received a prior cumulative dose of 300 mg/m^2 of DOX.(57) Later, several trials on the benefit-risk of DRZ have been published and indicate that DRZ is a well-tolerated and effective cardioprotectant. In 2017, after reassessment of the data, the contraindication for children and adolescents at risk for cardiotoxicity was removed.(58) The field of oncology has accepted the potential benefits of DRZ.(59) Recently, Liesse *et al*. generated predictions for treatment protocols with and without affiliated DRZ therapy. Noticeably, DRZ delayed the exponential rise in cardiotoxicity to doses of more than $400mg/m^2$, while without DRZ, the exponential rise in cardiotoxicity was observed with doses of more than $200mg/m^2$.(60)

6.1.5. Pharmacogenetics/pharmacogenomics

The field of pharmacogenetics has been defined as the study of variability in drug response due to heredity.(61) More recently the term 'pharmacogenomics' has been introduced, which includes all genes in the genome that may determine drug response.(62) Different genetic factors are known to influence the balance between DOX efficacy and toxicity. Indeed, inherited differences in drug targets, metabolizing enzymes and transporters will influence pharmacokinetics and –dynamics of drugs and will determine the drug effects.(63) Pharmacogenomics has been widely recognized as fundamental steps towards personalized medicine, which is of utmost importance for patients with high risk of developing cardiotoxicity from anthracyclines.(64) Leong et al. indicated that several polymorphisms of pharmacogenetics candidates across the anthracyclines biochemistry and cardiomyopathy pathways are potentially a predictor for anthracycline-induced cardiotoxicity. However, the evidences are limited and further studies are needed to generate robust genetic predictor(s).(65)

6.1.6. Cardioprotective drugs for primary prevention–clinical update

DRZ is the only pharmacologic agent that is approved by the FDA to prevent cardiotoxicity in patients receiving anthracyclines.(56) However, to date, beta-blockers, renin-angiotensin inhibitors and statins have demonstrated promising results in studies evaluating their efficacy in primary prevention (Table 2).(35) Indeed, both randomized and observational data demonstrate a potential cardioprotective role in patients receiving chemotherapy.(66-72) Two randomized trials recently tested whether primary prevention using these drugs during chemotherapy can reduce cardiotoxicity and preserve LVEF.(73, 74) Additionally, statins seem to have protective effects during chemotherapy based on a small randomized trial and observational studies.(75-77) However, there are significant

limitations, including small sample size, low event rate, and short follow-up period. The modest effect on LVEF in the treatment groups must be analysed in the context of the relative lack of data concerning the natural history of asymptomatic LV dysfunction in cancer patients receiving cardiotoxic drugs.(35) Large multicenter studies that include hard clinical endpoints such as symptomatic HF and cardiovascular death are needed.(35, 78)

6.2. Secondary prevention of cardiotoxicity from anthracyclines

Secondary prevention requires that patients be monitored during and after treatments and be managed when cardiotoxicity signals appear.(79) Difficulties in defining cardiotoxicity at a molecular level translate into uncertainties in clinical settings. This prevention may be conducted by a combination of imaging studies and biomarkers, and may form the rationale for starting cardioprotective treatment as soon as early signs of "cardiotoxicity" are identified.(4, 35) Cardiac dysfunction is detected as LVEF changes , which are measured by echocardiography (Tissue Doppler (80), longitudinal strain (81)) , multigated radionuclide angiography (82), or magnetic resonance imaging (83). Blood cardiac biomarkers are used to identify cardiotoxicity while receiving therapy. Increases in cardiac troponins reflect myocardial injury and chronic increases in natriuretic peptides indicate ventricular wall stress.(84-86) Both represent an effective method for monitoring cardiac status, and identifying patients who may benefit from early medical intervention. Unfortunately, clinically apparent signs of cardiac injury often arise years after initial therapy. Early rises in biomarker concentrations are difficult to link with clinical endpoints. Indeed, there is a need for long-term data to either confirm or refute any relationship between early biomarkers and long-term cardiac morbidity.(87) Further, the European Society of Cardiology guidelines recommended an aggressive therapeutic approach of LV dysfunction even in asymptomatic patients after anthracycline therapy, consisting of angiotensin converting enzyme inhibitor (ACEI) or Angiotensin II receptor blockers (ARBs) and

beta-blockers. Depending upon the magnitude of the decrease and the LVEF value, initiating one or more guideline-based HF therapies should be considered.(78) Indeed, Yun et al. demonstrated that ACEI and beta-blocker treatment were associated with better LVEF preservation, and the benefit was prominent in patients treated with higher accumulative dose of anthracyclines.(88) Unfortunately, many patients with asymptomatic decreased LVEF are not receiving American College of Cardiology / American Heart Association Class I-indicated beta-blocker or ACEI/ARB therapy.(89) Symptomatic patients presenting with clinical HF during or following chemotherapy should be treated with standard regimens for CHF, such as ACEI, beta-blockers, diuretics, digoxin and spironolactone.(78) However, it is not known yet if the same treatments are effective for childhood cancer patients and survivors with anthracycline-induced cardiotoxicity.(90)

7. Preclinical models of chemotherapy-induced cardiotoxicity

Small and large animal models, as well as *in vitro* models, have been used to study the pathophysiology of cancer therapy-induced cardiomyopathy and new cardioprotective therapies.(91) However, the pharmacodynamics actions of antineoplastic drugs in different animal species are variable.(38, 91, 92) DOX has been characterized in several animal species as a total dose-depend multifocal myocardial degeneration that occurs following either acute or chronic administration.(93) To simulate clinical scenarios and the actions of potential cardioprotectants, an experimental model of long-term administration with low anthracycline doses is required. Long-term studies of anthracycline cardiotoxicity should take precedence over short-term *in vitro* treatments of isolated cells, where the potential impact of factors such as plasma protein binding and tissue distribution cannot be assessed.(4, 94) Repeated administration of DOX causes cardiomyopathic changes in patient as well as in animal species.(94) Although small animals are readily available and easy to handle, results of studies evaluating cancer therapy-induced cardiomyopathy and its treatments in these models have

presented only limited predictive clinical value.(95, 96) However, despite species-related or model-dependent variances, valuable insights into the molecular mechanisms of antineoplastic drug-induced cardiomyopathy can be inferred.(38)

8. Conclusion

Anthracycline-induced cardiomyopathy is an important public health concern. To reduce the incidence, a deep understanding of its toxicity and mechanisms of action are crucial. There are some strategies to prevent the cardiac side effects, however, the only compound consistently found to be cardioprotective in experimental and clinical studies is the FDA-approved DRZ. Larger randomized controlled trails in examining functional imaging techniques, biological parameters, and genetic alterations, will be needed to ameliorate prediction, prevention and treatment of anthracycline-induced cardiotoxicity. In the emerging era of personalized cancer medicine, pharmacogenomics has been recognized as fundamental steps and may be effective to consign the cardiac effects of anthracycline to history. Anticancer drug-induced cardiotoxicity should be viewed as a multidisciplinary approach including basic science, oncological and cardiological expertise, since advances in cancer treatment have greatly improved survival rates of children and adults with cancer. As this issue is still under large debate and no clear and defined guidelines are yet available, oncologists and cardiologists must cooperate in the interest of best practice and the urgent need to prevent today's cancer patients from becoming tomorrow's cardiac patients.

Conflict of Interest

None.

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Tables

Mechanism	Main histological changes
Profibrotic effects of ROS	↑Fibroblast proliferation
	↑Transformation into myofibroblasts
	↑Expression of profibrotic genes
	Balance alterations between extracellular matrix destruction (by matrix metalloproteinases) and formation (collagen synthesis)
	LV fibrosis
Ultrastructural features	Loss of myofibrils
	Dilatation of the sarcoplasmic reticulum
	Cytoplasmic vacuolization
	Mitochondria swelling
	↑Number of lysosomes
Proteolysis	Loss of integrity or function of titin
Apoptosis	DNA degradation
	Nuclear fragmentation
	Chromatin condensation
	Mediated part by p38 MAPK activation
Autophagy	Formation of polyubiquitin-positive inclusions
	Downregulation of proteasome activity
	Accumulation of oxidatively damaged macromolecules and organelles

Table 1: Anthracyclines histological pathophysiology.

Year/Reference	Chemotherapy/Cancer type	Primary prevention	Patients/Duration	Results
Beta-blockers (BB) and angiotensin-receptor inhibitors (ACEI)/ angiotensin-receptor blocker (ARB)				
2018 Ref:(97)	Anthracycline in HER2-negative breast cancer	Carvedilol (BB) vs. Placebo	200; 6 months	Treatment: LVEF – 0.9% Placebo: LVEF – 1.3% (p=0.84)
2013 Ref:(73)	Anthracycline therapy against malignant hemopathies	Enalapril (ACEI) + carvedilol (BB) vs. Placebo	90 (45treatment; 45placebo); 6 months	Treatment: LVEF – 0.17% Placebo: LVEF – 3.28% (p = 0.04)
2015 Ref:(74)	Anthracycline +/- trastuzumab in early breast cancer	2x2 factorial: candesartan (ARB), metoprolol (BB) vs. Placebo	120; 10-61 weeks	Candesartan: LVEF – 0.8% Placebo: LVEF –2.6% (p = 0.026)
2014 Ref:(66)	Anthracycline in breast cancer	Carvedilol (BB) vs. Placebo	80 (40BB; 40placebo); 6 months	LVEF no Δ Tissue Doppler peak systolic strain and strain rate ↓ in control vs. carvedilol (p < 0.005)
2013 Ref:(67)	Anthracycline + trastuzumab in breast cancer	1:2 propensity matched	318 (n=106BB; n=212control); 3.2±2.0 years	Treatment: HF 5% (n = 5) Control: HF 13% (n = 27) (p = 0.008)
2013 Ref:(68)	Anthracycline in breast cancer	Nebivolol (BB) vs. Placebo	45 (n=27BB; n=18placebo); 6 months	Treatment: LVEF 65.6 → 63.8 Placebo: LVEF 66.6 → 57.5% (p = 0.01)
2010 Ref:(69)	Doxorubicin-treated lymphoma	1:1:1 Metoprolol (BB), enalapril (ACEI), control (no	125 (n=42BB; n=43ACEI; n=40control); 31 months	Metoprolol: HF 2% (n = 1) Enalapril: HF 5% (n = 2)

		treatment)		Control: HF 8% (n = 3) (p = 0.55)
2010 Ref:(70)	Epirubicin against multiple cancers	Telmisartan (ARB) vs. placebo	49 (n=25ARBs; n=24placebo); 3 months	Strain rate normalized with Telmisartan
2006 Ref:(71)	Anthracycline in lymphoma and breast cancer	Carvedilol (BB) vs. control (placebo)	50 (n=25BB; n=25control); 6 months	Treatment: LVEF 70.5 → 69.7% Control: LVEF 68.9 → 52.3% (p < 0.001)
2005 Ref:(72)	Anthracycline in untreated non-Hodgkin lymphoma	Valsartan (ARB) vs. control (placebo)	40 (n=20ARB; n=20control); Analysis after 0-3-5-7 days of chemo initiation	Valsartan prevented ↑ in LV end-diastolic dimension
Statins				
2015 Ref:(75)	Anthracyclines in breast cancer, leukemia or lymphoma	Statin vs. Placebo	51 (n=14statin; n=37placebo); 6 months	Treatment: LVEF -1.1%; Placebo: LVEF -6,5% (p=0.03)
2012 Ref:(76)	Anthracycline +/_ trastuzumab in breast cancer	1:2 propensity matched	201 (n=67statin; n=134control); 2.6±1.7 years	Treatment: HF 6% (n=4); Control: HF 17% (n=24) (p=0.04)
2011 Ref:(77)	Anthracycline therapy against malignant hemopathies	Atorvastatin vs. Placebo	40 (n=20statin; n=20placebo); 6 months	Treatment: LVEF +1.3% Placebo: LVEF -7.9% (p<0.001)
Aldosterone inhibitors				
2015 Ref:(98)	Anthracycline therapy in breast cancer	Spirinolactone vs. Placebo	83 (n=43spirinolactone; n=40placebo); 25 weeks	Treatment: LVEF 67.0 → 65.7% (p=0.094) Placebo: LVEF 67.9 → 53.6% (p<0.001)

Table 2. Selected Publications: Primary Prevention in Patients without cardiac dysfunction