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Review Article

# Duxorubicin-induced cardiotoxicity

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## ABSTRACT

The survival rate of cancer patients has greatly increased over the last 20 years. However, to achieve this result, a considerable price has been paid in terms of the side-effects associated with the intensive anticancer treatment. Cardiotoxicity of anticancer drugs is a serious problem. It is defined, by the National Cancer Institute, as the "toxicity that affects the heart." This definition not only includes a direct effect of the drug on the heart, but also an indirect effect due to enhancement of hemodynamic flow alterations or due to thrombotic events. Cardiotoxicity can develop in a subacute, acute, or chronic manner. The risk for such effects depends upon: cumulative dose, rate of drug administration, mediastinal radiation, advanced age, younger age, female gender, pre-existing heart disease and hypertension. Anthracyclines, such as doxorubicin (DOX), cause serious cardiac side-effects. Acute tachyarrhythmias and acute heart failure (HF) may occur after high doses, but these reactions are now rare due to changed dosage schemes (e.g. slower infusion) with the aim to prevent this. However, the sub-acute or chronic cardiac effects of anthracyclines remain a clinical problem. Clinically, anthracycline induced cardiotoxicity manifests itself as left ventricular failure, which develops insidiously over months to years after completion of the anthracycline based chemotherapy and may result in congestive HF. The mechanism of anthracyclin induced cardiotoxicity is not totally unraveled. It is likely that the decline in myocardial function is related to apoptosis of cardiac myocytes that occurs apparently at random in the myocardium. Anthracyclin induced formation of reactive oxygen species (ROS) in the presence of intracellular iron, impaired homeostasis of intracellular iron and calcium (that may facilitate the apoptosis induced by the ROS) have been put forward as mechanisms. Cardiac protection can be achieved by limitation of the cumulative dose. Further, addition of the antioxidant and iron chelator dexrazoxane to anthracycline therapy has shown to be effective in lowering the incidence of anthracycline induced cardiotoxicity.

**Keywords:** Cardiotoxicity, Cytotoxic drugs, Cancer, Chemotherapy, Anthracyclines, Duxorubicin

## INTRODUCTION

Cancer therapy has substantially improved over the past decade with the introduction of combination drug regimens, adjuvant and targeted therapies. As a result, patients in increased numbers and in older age undergo chemotherapy with a significantly increased survival. However, the spectrum of cardiac side-effects associated with these progresses has also gradually expanded, including increased recognition of additive cardiac toxicity of anticancer drugs in combination and identification of previously unsuspected concerns associated with the widespread use of recently introduced targeted therapies.[1] Cardiotoxicity of anticancer drugs is a very significant problem. As defined, by the National Cancer Institute, the "toxicity that affects the heart." The definition includes a direct effect of the drug on the heart and also an indirect effect due to enhancement of hemodynamic flow alterations or due to thrombotic events.[2] The use of chemotherapeutic agents, radiation (RT) therapy, and molecular targeted therapies are all gateway reasons that can injure the cardiovascular system, both at a central level by deteriorating the heart function and in the periphery by enhancing hemodynamic flow alterations and thrombotic events often latently present in oncology patients. Unluckily, a comprehensive analysis of published data on cardiotoxicity is difficult to perform and would be inadequate because oncology trials measuring vascular effects vary widely in their methods and definition of cardiotoxicity.[3]

## CHEMOTHERAPY INDUCED CARDIOTOXICITY

Cardiotoxicity may depend on the dose administered during each course or on the total cumulative dose, or may be completely independent of the dose like anthracycline-induced cardiotoxicity, which has been recognized for more than 20 years. It has been described as three distinct types of cardiotoxicity. Acute or sub-acute injury is a rare form of cardiotoxicity that may occur immediately after a single dose or a course of anthracycline therapy, with clinical manifestations occurring within a week of treatment. These may be in the form of transient electrophysiological abnormalities, a pericarditis, myocarditis syndrome or acute left ventricular failure. The electrophysiological abnormalities may present as nonspecific ST and T-wave changes, T-wave flattening, decreased QRS voltage and prolongation of QT interval. Sinus tachycardia is the most common rhythm disturbance. Electrocardiogram (ECG) changes may be seen in 20-30% of the patients.[4] Arrhythmias, including ventricular, supraventricular and junctional tachycardia, are seen in 0.5-3% of patients with an overall incidence of 0.7%.[4] More serious arrhythmias, such as atrial flutter or atrial fibrillation, are rare. Sub-acute cardiotoxicity has resulted in acute failure of the left ventricle, pericarditis or a fatal pericarditis-myocarditis syndrome in some rare cases. The ECG changes or arrhythmias do not seem related to chronic cardiomyopathy. Early onset chronic progressive cardiotoxicity: anthracyclines can also induce early onset progressive chronic cardiotoxicity resulting in cardiomyopathy. This is a more common and clinically important type of cardiotoxicity.[5] Chronic anthracycline-induced cardiomyopathy usually presents within a year of treatment. It may persist or progress even after discontinuation of anthracyclines therapy, and may evolve into a chronic dilated cardiomyopathy in adult patients and restrictive cardiomyopathy in pediatric patients.[6] Late onset chronic progressive anthracycline cardiotoxicity causes ventricular dysfunction,[7] heart failure (HF) and arrhythmias[8] years to decades after chemotherapy has been completed. This suggests that patients who have received anthracyclines chemotherapy and survived their cancer may have undetected increases in morbidity and mortality due to cardiotoxicity. There may be a period of time, after completion of treatment, during which patients may experience no symptoms of left ventricular dysfunction or arrhythmia, and cardiac function may appear normal. After the initial acute myocardial insult, there is a progressive decrease in ventricular function leading to late onset decompensation. An increased incidence of severe echocardiographic (ECHO) abnormalities has been seen with increased duration of follow-up. An 18% incidence of reduction in fractional shortening on resting ECHO was observed 4-10 years after completion of anthracycline therapy.[8] Cumulative doses of DOX as low as 228 mg/m$^2$ have shown to increase after-load or decrease contractility, or both, in 65% of patients with leukaemia up to 15 years after treatment with anthracyclines.[9] Late onset arrhythmia and sudden death have occurred more than 15 years after anthracycline treatment.[10] This could mean that more anthracycline induced cardiotoxicity may appear in the future in patients who are presently asymptomatic. Patients may remain in a compensated state for many years until stressors such as acute viral infection[11] or cardiovascular stressors such as weight lifting, pregnancy and surgery could possibly trigger a cardiac event.[8]

Although several drugs are potentially cardiotoxic (Tables 1 and 2), the drugs most commonly associated with cardiotoxicity are anthracyclines (DOX and epirubicin), taxanes, alkylating agents, and trastuzumab, which belongs to the class of monoclonal antibodies against human epidermal receptor-2 that has recently been introduced in treatment of advanced breast cancer. Newly introduced non-receptor tyrosine kinase inhibitors,[10] which induce modifications in cardiomyocyte cultures and in animal models, can possibly determine cardiotoxicity in patients treated for cancer as well, but the question is still being debated.[13]

### *Anthracyclines and cardiotoxicity*

Anthracyclines are widely used antineoplastic agents for the treatment of both childhood hematological malignancies and solid tumors, including acute lymphoblastic leukaemia. The significant improvement in the outcome of childhood acute lymphoblastic leukaemia in recent decades[14] means that the risk of anthracycline-induced cardiovascular disease is now a major concern for the growing number of survivors. Anthracycline-related cardiotoxicity may be manifested by early/acute changes or by delayed/late-onset

**Table 1: Chemotherapeutic drugs with cardiovascular manifestations.[12]**

| Chemotherapeutical drug | Cardiovascular manifestations |
|---|---|
| Anthracyclines | LV dysfunction, HF, myocarditis, arrhythmia |
| 5-fluorourcil | Ischemia, HF, pericarditis, carcinogenic shock |
| Taxanes (paclitaxel), vinca alkaloids | Sinus bradicardia, ventricular tachycardia, atrioventricular block, heart failure, ischemia |
| Cyclophosphamide | HF (neurohumoral activation), mitral regurgitation |
| Trastuzumab | LV dysfunction, HF, arrhythmia |
| Tamoxifen | Thromboembolism, cholesterol metabolism anomalies |
| Bevacizumab | Hypertension, thromboembolism |
| COX-2 specific inhibitors | Thromboembolism |

HF: Heart failure, LV: Left ventricular, COX = 2: Cyclooxygenase

**Table 2: Chemotherapeutic drugs with potential cardiotoxic effects.[13]**

| | |
|---|---|
| Antibiotics cytotoxic | Anti-microtubule agents |
| Anthracyclines | Paclitaxel |
| DOX | Docetaxel |
| Daunorubicin | Etoposide |
| Epirubicin | Teniposide |
| Idarubicin | Vinca alkaloids (vinorelbine) |
| Mitoxantrone | Monoclonal antibodies |
| Bleomycin | Trastuzumab |
| | Rituximab |
| Alkylating agents | Tyrosine kinase inhibitors |
| Cyclophosphamide | Imatinib mesylate |
| Ifosfamide | Sunitinib |
| Cisplatin | Miscellaneous |
| Mitomycin | Tretinoin |
| Busulfan | Pentostatin |
| Antimetabolites | Interferon |
| 5-fluorouracil | Interleukin 2 |
| Capecitabine | |
| Methotrexate | |
| Fludarabine | |
| Cytarabine | |

cardiotoxicity. Acute clinically symptomatic toxicity is rare. More commonly, anthracyclines induce progressive chronic cardiotoxicity.[15] This effect is cumulative and dose-related, increasing with cumulative doses of 300 mg/m$^2$ or more.[16] However, susceptibility to this complication is largely individual, and one subset of patients shows signs of cardiomyopathy even at a low cumulative dose.[17] Once symptoms of congestive HF (CHF) develop, the discontinuation of anthracycline treatment may not reverse this condition. The only effective way to avoid late cardiotoxic effects appears to be to prevent early cardiac injury during chemotherapy. Currently, echocardiography is used to monitor the heart function during DOX therapy, but it often fails to allow the early signs of cardiotoxic side-effects to be detected. Recent studies have demonstrated that the myocardial performance index is a sensitive non-invasive Doppler measurement of global (systolic and diastolic) ventricular function. This index allows the cardiac "reserve" to be assessed and facilitates earlier detection of myocardial dysfunction, allowing subclinical dysfunction in children and adults to be detected. In addition, currently there is growing interest in the use of biomarkers for the detection of cardiac injury. Elevation of biochemical markers such as N-terminal pro-brain natriuretic peptides and cardiac troponin-T (cTnT) have been suggested as surrogates for anthracycline-induced myocardial injury. However, the diagnostic value of all these parameters in the early assessment of preclinical anthracycline cardiotoxicity remains largely undefined.[18]

Anthracyclines are known for their strong cardiotoxic effects, predominantly HF and cardiomyopathies. Standard and periodic measurements of left ventricular ejection fraction (LVEF) are thus essential. ECHO or a multiple gated acquisition (MUGA) scan should be performed at baseline for proper assessment of LVEF. MUGA, a non-invasive procedure used to measure cardiac function, can locate a part of the heart muscle that has been damaged and evaluate the type of damage. ECHO uses sound waves to produce images of the heart to determine how fast the heart is beating and pumping blood. Anthracycline associated cardiotoxicity is cumulative and permanent (Table 3). There are three types of, Anthracycline associated cardiotoxicity as, immediate, early-onset, and chronic progressive cardiotoxicity. The primary risk factor for anthracycline associated cardiotoxicity. It is the cumulative lifetime dose of the anthracycline. The cumulative lifetime dose must be documented and retained for proper drug dosage, patient safety, and positive therapeutic outcomes. Patients are predisposed to the development of cumulative lifetime dose when the cumulative lifetime dose is exceeded. The main mechanism of action for anthracycline associated cardiotoxicity is hypothesized to be the generation of oxygen free radicals, which cause oxidative stress, resulting in cellular damage in the cardiomyocyte and eventually apoptosis, which is directly correlated with the dose of anthracycline administered (Figure 1). Iron accumulation occurs through both enzymatic and non-enzymatic channels precipitated by free-radical generation and redox-associated injury to the cardiomyocyte. As mitochondrial damage occurs, calcium levels rise, inhibiting the action of the sarcoplasmic reticulum (SR) and decreasing the function of the sodium-potassium pump. All of these factors are implicated in anthracycline associated cardiotoxicity.[19-25] Risk factors include prior anthracycline therapy, the drug's chronic liver disease, younger age at treatment initiation, current pregnancy, DOX dose ≥300 mg/m$^2$, epirubicin ≥600 mg/m$^2$, mediastinal RT, combination ChT regimens, and increased overall survival.[19-24]

### *Risk factors*

Cardiac abnormalities that develop during a long follow-up period after anthracycline therapy may be exacerbated in middle age and elderly patient who are already prone to cardiac diseases. General risk factors for cardiovascular diseases such as hypertension, hyperlipidaemia and diabetes may contribute to the progression of cardiac damage.[27] Smoking similarly causes a severe oxidative stress that increases the risk of cardiovascular diseases, especially in women. Female sex is generally associated with a remarkable, about two-fold, increase in cardiac morbidity and mortality once a cardiac risk factor is established. Interestingly, the increased susceptibility to anthracycline in female is also observed with diabetes and after thrombolytic therapy although primary cardiac events prevail in male. Older women and younger women show similar reductions in mortality due to chemotherapy for

**Table 3: Anthracycline and their cumulative life time dose.[19-25]**

| Anthracycline | Indication | Cumulative life time dose |
|---|---|---|
| DOX (adriamycin) | Bladder cancer, breast cancer, endometrial cancer, hepatoblastoma, leukemia, SCLC, lymphoma, multiple myeloma, neuroblastoma, osteosarcoma, ovarian cancer, prostate cancer, sarcoma, Wilms' tumor | 450 mg/m$^2$ |
| Liposomal DOX | AIDS-KS, multiple myeloma, ovarian cancer | 550 mg/m$^2$ |
| Daunorubicin | Acute lymphoblastic leukemia, acute myelogenous leukemia | 400 mg/m$^2$ in adults receiving chest RT, 500 mg/m$^2$ in patients with cardiotoxic risk factors |
| Epirubicin | Breast cancer, esophageal cancer, gastric cancer | >900 mg/m$^2$ |
| Idarubicin | Acute myelogenous leukemia | >160 mg/m$^2$ |

AIDS-KS: AIDS related Kaposi sarcoma, RT: Radiation, SCLC: Small cell lung cancer, DOX: Doxorubicin

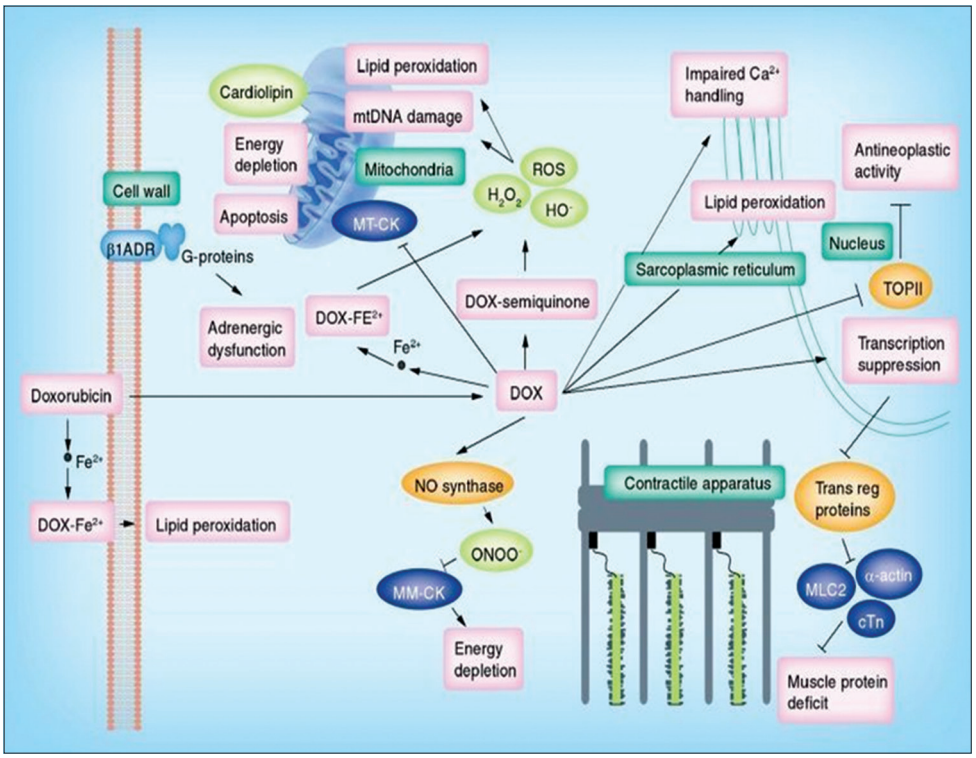


**Figure 1: Mechanism of anthracycline toxicity within the cardiomyocyte.[26] Anthracyclines enter cardiomyocytes by passive diffusion and spur the generation of free radicals, leading to cell damage. Anthracyclines also directly and indirectly inhibit gene transcription, mitochondrial functioning, and energy production within the cell. β1ADR: β1 adrenergic receptor; Ca: Calcium; cTn: Cardiac troponin; DOX: Doxorubicin; $Fe^{2+}$: Iron; MLC2: Myosin light chain; MM-CK: Muscular creatine kinase; MT-CK: Mitochondrial creatine kinase; NO: Nitric oxide; ROS: Reactive oxygen species; TOPII: Topoisomerase II; Trans reg: Transcriptional regulatory.**

breast cancer, and a chemotherapy in older women who are in good health.[28] However, few studies have been focused on the impact of sex on cardiotoxicity. It has also been clearly documented that local RT therapy increases the risk to develop cardiovascular pathologies.[29] Strongly supporting the contention those alterations of the resident myocardial cell turnover is an important factor in the development of cardiotoxicity. Importantly, recognition of genetic and proteomic markers of individual patient susceptibility to the cardiotoxic effects of anthracyclines could improve the safety of this treatment.[19]

***Duxorubicin***

In, early 1960s duxorubicin was first isolated. It remains among the most effective anticancer drug ever developed. Anyhow, this drug has proven to be a double-edged sword because it also causes a cardiomyopathy that leads to a form of CHF that is usually refractory to common medications. Cardiotoxicity is reported in 14-49% of patients treated for lymphoma, and among patient with non-Hodgkin lymphoma, the risk of CHF increases with the patient's age and history of coronary heart disease,

valvular heart disease, hypertension, diabetes, cigarette smoking, or obesity.[28] It is hoped that a better understanding of the mechanisms underlying DOX's cardiotoxicity will enable the development of therapies with which to prevent and/or treat the HF it causes. Suggested contributors to DOX-induced cardiomyopathy include formation of reactive oxygen species, apoptosis, inhibited expression of cardiomyocyte-specific genes, and altered molecular signaling. And taking these various contributors into consideration, a variety of approaches aimed at preventing or mitigating the cardiotoxicity of DOX have been tried, but so far, the ability of these treatments to protect the heart from damage has been limited. That said, one recent approach that shows promise is adjuvant therapy with a combination of hematopoietic cytokines, including erythropoietin, granulocyte colony-stimulating factor, and thrombopoietin. This approach, to preventing DOX-induced cardiomyopathy, is worthy of serious consideration for clinical use. Some biochemical markers seem to be useful for early detection of anthracycline induced cardiotoxicity and for identifying the patients at risk for cardiotoxicity in future. Although cTnTs are known to be elevated mainly in patients with acute myocardial infarct, unstable angina, CHF and myocarditis, they have been reported to be potentially useful markers for the early detection of anthracycline induced cardiotoxicity.[30] Lipshultz et al. found elevated serum cTnT levels in children treated with DOX, and the degree of cTnT elevation predicted left ventricular dilatation and wall thinning 9 months later, suggesting that an elevated cTnT level may predict subsequent subclinical and clinical cardiac morbidity.[31] Missov et al. reported elevated cTnI levels in 13 patients who had been treated with anthracyclines. However, the elevations were at low levels, the probable result of prolonged release of cTnI into plasma from initial myocardial injuries and a decrease in ability to recover. This low-level increment was termed sub-myocardial infarction range (0-10 ng/ml). Seino and colleagues found elevated serum cTnT levels in rats given 1.5 mg/kg/week DOX 8 times.[32] Herman et al. found elevated serum cTnT levels with increments in cumulative doses and a correlation between average cTnT levels and cardiomyopathy scores in rats. They proposed that determining serum levels of cTnT is a sensitive means for assessing the early cardiotoxicity of DOX.[33]

However, Kismet et al.[34] found no correlation between serum cTnT levels and cumulative DOX levels in 24 patients treated with DOX. In addition, they showed no correlation between serum cTnT levels and ECHO detected systolic and diastolic findings. In that study, all of the patients had been given DOX at cumulative doses of ≥400 mg/m$^2$. Researchers investigated whether cumulative DOX administration-related myocardial cell damage can potentially increase cTnI levels above the expected values. In healthy individuals, they are expected to be under the detection limit. Although cTnI is a recently described sensitive biomarker for the detection of minor myocardial damage, its blood level was undetectable both in patients with cumulative DOX doses ≥400 mg/m$^2$ and in patients with cumulative DOX doses <400 mg/m$^2$. All values from both groups were within the ranges expected in healthy individuals. The main finding was that there was no association between serum cTnI levels and cumulative DOX doses in patients treated with DOX. It does not seem reliable to make a correlation between serum cTnI levels and cumulative DOX dose. One patient had impaired systolic cardiac functions, and two of the patients had impaired diastolic cardiac functions with a cumulative DOX dose of 450 mg/m$^2$, but none of the patients had detectable serum cTnI levels. It also seems that there is no relationship between low-level subclinical myocardial damage detectable by echocardiography and serum cTnI levels. Generally speaking, cardiotoxicity with cumulative doses above 450 mg/m$^2$ is a well-known adverse effect of DOX.[34] Lipshultz et al. reported no elevation of serum cTnT levels after discontinuation of anthracycline therapy, but the cumulative DOX doses of their patients were below 222 mg/m$^2$ and the number of the patients was very few. They found a low level serum cTnT elevations in patients continuing their DOX therapies and suggested that these low-level elevations may persist for a time as an indicator of chronic inflammatory changes. cTnTs potential role as a predictive factor in monitoring anthracycline therapy is not clear. Results support the claim that serum cTnT elevation due to long-term anthracycline therapy is much lower than the elevations reported in acute myocardial injuries as a result of prolonged release of cardiactroponin into plasma and a decrease in ability to recover. The use of cTnI with increased analytical sensitivity to detect the low levels may demonstrate predictive value in delineating the high risk group of anthracycline induced cardiotoxicity patients. A single measurement should not be relied on; serial measurements may provide useful information for accurate diagnosis because the deterioration in cardiac functions may appear months or years after the DOX treatment. Although echocardiography may not detect early myocardial damage, it is still a non-invasive, practical and reliable method to identify consistent changes in cardiac performance.[30]

## POTENTIAL MECHANISMS OF DOX-INDUCED CARDIOTOXICITY

There have been several proposed mechanisms for DOX-induced cardiotoxicity (Figure 2), (a) Free radical generation and oxidative stress, (b) increased cardiomyocyte death by necrosis and apoptosis, (c) inhibition of cardiac specific muscle gene transcription and translation, in combination with an increase in myofibril protein degradation, leading to loss of myofibrils and, (d) disturbance of intracellular calcium homeostasis.[35] Studies have been conducted to investigate DOX-induced cardiomyocyte apoptosis in H9c2 rat embryonic cardiomyocytes, neonatal and adult rat cardiomyocytes, as well as in hearts from rats and mice treated with DOX.

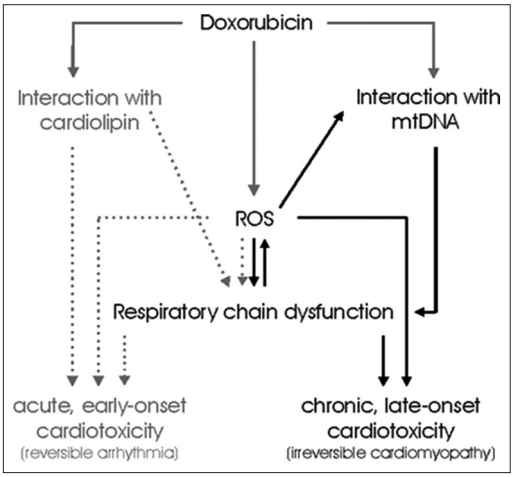


**Figure 2: Proposed mechanisms of doxorubicin cardiotoxicity.[36]**

DOX induces apoptosis via both intrinsic and extrinsic pathways. DOX alters the ratio of pro-apoptotic and anti-apoptotic Bcl-2 family proteins, including Bcl-2, Bad, Bim, Bax, Bak and Bik. It also causes DNA damage and p53 activation. All these changes can cause loss of mitochondrial integrity, the leakage of cytochrome C and the activation of caspase 9. Mitochondrial dysfunction is an early indicator of DOX-induced apoptosis in cardiomyocytes. Within the extrinsic pathway, DOX increases Fas and FasL, followed by the activation of caspase 8.[37,38] The activation of caspase 9 and/or caspase 8 eventually leads to the activation of caspase 3, cleavage of genomic DNA and apoptosis.[39] DOX selectively down-regulates cardiac specific muscle gene expressions. These may involve decreases in cardiac muscle gene transcription and translation, as well as increases in selective proteasome degradation of these proteins.[40] Studies have shown that DOX decreases the expression of sarcomeric actin, cTnI, and myosin light chain 2.[41] DOX treatment decreases cTnTs in left ventricular tissues of mice and in cultured rat neonatal cardiomyocytes down-regulations of cTnTs by DOX are caused by decreased transcription and translation as well as increased caspase and proteasome degradation of these proteins caspase 3, 5, 6 or 10 directly cleaves cTnTs, while caspase 9 or 13 may indirectly cause degradation of these proteins.[42] Other reports also have shown that DOX inhibits the expression of transcription factors or cofactors that are important for regulation of cardiac-specific gene transcription. These include GATA4, myocyte enhancer factor-2C, dHAND, Nkx2.5 and p300.[40,43] In addition to cardiac genes, GATA4 may also regulate genes that are involved in the process of apoptosis. Overexpression of GATA4 in cardiomyocytes or mouse hearts attenuates DOX-induced apoptosis. On the other hand, GATA4 null mice are more susceptible to DOX cardiotoxicity.[43] In addition to myofibril loss, DOX also induces myofibril disarray in cardiomyocytes.[44] Degradation of titin, a myofilament protein, may contribute to this effect of DOX. Titin is a scaffold protein that assembles myofilament proteins into sarcomeres. It regulates cardiomyocyte contractile function via length dependent activation in stretched sarcomeres during the transition from diastole to systole,[45] activates calcium dependent proteases calpains which in turn cause titin degradation.[46]

The SR $Ca^{2+}$ pump (SERCA2a) plays a pivotal role in intracellular calcium mobilization and thus myocardial contractility. The SR or chest rates the movement of calcium during both contraction and relaxation of the heart. Excitation leads to the opening of voltage gated L-type calcium channels, allowing the entry of calcium, which then stimulates the release of a much larger amount of calcium from SR and subsequent contraction. During relaxation, calcium is re-sequestered into SR by SERCA2a and extruded to the extracellular fluid by the sarcolemmal sodium-calcium exchanger.[47,48] A decrease in SERCA2a ATPase activity and $Ca^{2+}$ uptake is responsible for the abnormal $Ca^{2+}$ homeostasis in human cardiomyocytes from failing hearts.[49,50] Studies have shown that DOX can either increase or decrease cardiomyocyte contractility. The discrepancy of these findings may be caused by different animal and cell culture models, the dosage of DOX, the duration of the treatment and especially the developmental stage of the disease. In the early stage of the disease, DOX tends to induce $Ca^{2+}$ release from SR and increase cardiomyocyte contractility. In the late stage of the disease, DOX inhibits $Ca^{2+}$ regulatory proteins and reduces cardiomyocyte contractility. In a subacute DOX mouse model, DOX induces an increase in cardiac contractile function as measured by dP/dtmax and dP/dtmin during the first few days after the DOX injection; however, cardiac function declines later on these results are consistent with the findings in DOX-treated patients.[35] DOX-induced reduction of cardiomyocyte contractility is often associated with decreased expression of SERCA2a.[51-53] Suggesting that impaired SERCA2a function may contribute to DOX-induced cardiomyocyte contractile dysfunction. Studies in mice with cardiomyocyte-specific overexpression of SERCA2a, however, showed that SERCA2a overexpression exacerbated DOX-induced mortality and morphological damage to cardiac tissue.[54] These results may be caused by constitutive activation of SERCA2a, especially during the early stage of DOX cardiac injury. Increase of SERCA2a activities at the early stage of the disease may further aggravate the adverse effects of DOX on $Ca^{2+}$ homeostasis, thereby exacerbating the disease. On the other hand, activation of SERCA2a at a later stage of the disease may be beneficial.[35]

## MANAGEMENT OF CHEMOTHERAPYINDUCED CARDIOTOXICITY

Currently, there are no guidelines developed specifically for the treatment of chemotherapy induced cardiotoxicity. However a few small studies support the use of neurohormonal antagonists in the treatment and prevention of this

pathology. Large, multi-centers trials are needed to establish guidelines for chemotherapy induced cardiotoxicity. A close collaboration between the cardiologist and oncologistis strongly recommended in order to establish a specific management for the patients. In addition to decreasing the cumulative dose of anthracyclines, there are other approaches that may reduce the risk of developing cardiac cells death. The administration of anthracyclines as infusions rather than as boluses, or the liposomal encapsulation of DOX is all measures which may help reducing cardiac toxicity.[55] Dexrazoxane, an ethylene diamine tetra acetic acid like chelator, may reduce the risk of cardiotoxicity in association with DOX orepirubicin. However, its use is limited to patients who receive a cumulative dose of DOX >300 mg/m$^2$.[56] On the other hand, carvedilol, a beta-blocker with antioxidant properties, might reduce the risk of anthracyclines induced cardiotoxicity. Kayan et al. demonstrated in 50 patients receiving anthracycline therapy and either carvedilol 12.5 mg once daily or placebo, that there was no change in the LVEF in the carvedilol after 6 months. However, LVEF significantly decreased in the placebo group. Due to the small size of this study, additional larger trials are needed.[57] Cardinale et al. randomized 114 high risk patients with elevated troponin I after receiving high dose anthracyclines, to receive either enalapril at a starting dose of 2.5 mg daily or placebo for 1 year. 43% of the control group had a decrease in the LVEF compared to 0% in the enalapril group.[58] Overall, once the diagnosis of the chemotherapy-induced cardiotoxicity is established, the oncologist and cardiologist should discuss the patient's prognosis while weighing the risks of discontinuing the cardiotoxic agent. The initiation of standard HF treatment, as well as the discontinuation of the cardiotoxic agent, will increase the recovery of LV function.[35]

Attempts to minimize the cardiotoxicity of anthracyclines include dose limitation, schedule modification, use of less cardiotoxic analogues, and use of cardio protective agents. Liposomal formulations of anthracyclines remain the best known alternative for improving the index and spectrum of activity with less cardiotoxicity of DOX in clinical use.[13] There is an urgent need for large multicenter trials in order to validate some of the preliminary albeit promising research, already conducted in this field.

## CONCLUSIONS AND FUTURE PROSPECTIVES

Anthracyclines are well known for their cardiotoxic side effects and comprehensive research is done to explore the mechanism of anthracycline induced cardiotoxicity. Until now the most accepted hypothesis is the so-called "free radical" theory. However, protective measurements following this theory such as administration of free radical scavengers have not appeared to be clinically successful. The approach of cardiologists to the definition of disease is quite different from that of the oncologists. Therefore, to perform interdisciplinary medicine, there is a risk that many concepts and observations may well be "lost in translation."[59] We feel that there is the need to train a generation of "cardio-oncologist" or "onco-cardiologist" investigators and clinicians to overcome these communication gaps. It is clear that for cancers with very poor prognosis, even with very aggressive therapy, cardiovascular risks fall to a lower priority. In cancers with high probability of long-term survival, such as breast and prostate cancers, it is very important to consider cardiovascular risks. For the vast majority of cancers that lie in-between, cardio-oncology needs to be brought increasingly into practice.

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