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Understanding Cardiomyopathy Induced by Doxorubicin Therapy: Mechanisms, Diagnosis, and Management Strategies

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Abstract

Doxorubicin-induced cardiomyopathy (DIC) is a significant complication of cancer treatment, characterized by irreversible cardiac damage and adverse effects on patient outcomes. Despite extensive research into its mechanisms and risk factors, effective prevention and management strategies still need to be discovered. This review summarizes the current understanding of DIC, including its epidemiology, mechanisms, clinical presentation, diagnosis, and prevention strategies. Emphasis is placed on the challenges in managing DIC, highlighting the need for novel therapeutic approaches targeting mitochondrial dysfunction, oxidative stress, and myocardial injury. Future research directions and advances in biomarker discovery are discussed, offering potential avenues for improving early detection and personalized management of DIC in cancer patients.

Keywords: Doxorubicin-induced cardiomyopathy; Anthracycline chemotherapy; Doxorubicin Cardiotoxicity; Cardiotoxicity; Cardiac surveillance

Abbreviations: DIC: Doxorubicin-Induced Cardiomyopathy; DOX: Doxorubicin; ROS: Reactive Oxygen Species; ECG: Electrocardiogram; LVEF: Left Ventricular Ejection Fraction; ACE: Angiotensin-Converting Enzyme; ARBs: Angiotensin II Receptor Blockers; CRT: Cardiac Resynchronization Therapy; ICD: Implantable Cardioverter-Defibrillator; FDA: Food and Drug Administration; JNKs: c-Jun N-terminal kinases; MRI: Magnetic Resonance Imaging; BNP: Brain Natriuretic Peptide; MIBG: Metaiodobenzylguanidine

Introduction

Doxorubicin is a product derived from the bacteria Streptomyces peucetius, belonging to the group of anthracycline antibiotics; it has cytotoxic activity, which gives it its antineoplastic characteristic. Doxorubicin also has a broad spectrum that is extremely useful in treating various types of hematological and tissue cancers like lung, bladder, ovarian, and thyroid [1]. Unfortunately, since the 1970s, studies have been published describing the side effects of doxorubicin therapy. Currently, its use is limited because of the significant impact on the quality of life of patients both in the short and long term, compromising

non-target organs at different levels, including the functioning of the cardiovascular, nervous, renal, hepatic, and hematological systems, in addition to affecting the fertility of patients, causing amenorrhea, premature menopause in women, testicular atrophy, oligospermia, and azoospermia in men [2,3].

Among all of these, the potentially fatal cardiovascular toxicity stands out; meta-analyses estimate that in a 9-year follow-up, at least 6% of patients treated with Doxorubicin develop clinical symptoms of cardiotoxicity, while 18% present a subclinical course [4]. It is associated with dose-dependent mitochondrial damage that results in deregulated mitochondrial dynamics, alteration of mitochondrial fusion, and imbalance of mitophagy. This side effect usually manifests within the first year. Pharmacological treatment clinically translates into a decrease in the left ventricular ejection fraction, dilated cardiomyopathy, and heart failure. Once the key points that cause research have been identified, they have proposed using therapies directed at the mitochondria to avoid cardiotoxicity caused by the antineoplastic drug. One strategy is using a mitochondrial fission inhibitor that interrupts the interaction between Drp1 and its receptors. Despite this, it is necessary to carry out more studies that delve into cardioprotective measures that can create a margin of safety for patients using Doxorubicin [5].

Mechanisms of Doxorubicin-Induced Cardiomyopathy

Doxorubicin is an anticancer drug from the anthracycline class used as a chemotherapeutic agent for many malignancies [6]. It achieves its anticancer effect by integrating into the DNA of the malignant cell, leading to DNA damage by inhibiting topoisomerase II, which subsequently induces apoptosis. Insertion into the DNA inhibits the synthesis of RNA and macromolecules, DNA cross-linking, and binding [7]. Combining Iron and Doxorubicin exacerbates the generation of reactive oxygen species (ROS), leading to further DNA damage [8,9]. Caution is advised when administering Doxorubicin as it has a well-known cardiotoxic effect, which can be irreversible and also fatal. The incidence of chronic doxorubicin-induced cardiomyopathy (DIC) is 1.7% [10]. This adverse effect can present within 30 days of administration or even 10 years post-treatment cessation. Morphologically, DIC presents with all four chambers dilated, reduced contractile function, and ventricular ejection fraction.

Subsequently, due to the alteration of the ventricle, wall thickness stress also increases [11]. Histologically, there are various characteristic presentations of DIC. Patchy myocardial interstitial fibrosis with adjacent Adria cells and scattered cardiomyocytes with abnormal vacuoles are classical. In addition, the loss of myofibrils and myofilaments makes the z-lines prominent. Commonly, myocyte vacuoles degenerate and coalesce to form large membrane-bound spaces [12]. These result from pathological mechanisms, such as oxidative stress, gene alteration, and apoptosis. It is important to note that doxorubicin toxicity targets the heart specifically due to its increased affinity for cardiolipin, a phospholipid exclusively located in the mitochondria, which generally increases in the heart due to its increased energy demand [13,14]. Doxorubicin binds to cardiolipin, located in the membrane of the mitochondria, subsequently impairing mitochondrial function as an anchor for cytochrome C [15]. This theory was confirmed when doxorubicin treatment displayed DIC-resistant outcomes in patients with Barths syndrome, a disease caused by the mutation of Tafazzin, a protein in cardiolipin, rendering them cardiolipin deficient [16]. There are various proposed mechanisms for DIC, such as inhibiting nucleic acid and protein synthesis or releasing vasoactive amines [17,18]. Similarly, alterations to the adrenergic and decreased antioxidant levels have been attributed to the pathophysiology of DIC [19,20]. The relevance and attributions these mechanisms have to DIC are yet to be established, but the main ones mentioned below are well-studied.

A characteristic finding in DIC is increased levels of ROS and lipid peroxidation, both of which point to oxidative stress being the primary pathophysiological mechanism in DIC [21]. Mitochondrial enzymes generate ROS, such as NADH dehydrogenase, cytochrome P450 reductase, and Xanthine oxidase [22,23]. Doxorubicin induces toxic damage to mitochondria, subsequently increasing ROS and generating more oxidative stress. Another mechanism of increasing oxidative stress is achieved through increasing endothelial nitric oxide synthase, subsequently promoting superoxide formation, which induces hydrogen peroxide formation [24,25]. Through this mechanism, Doxorubicin induces apoptosis [26]. Intracellular oxidants induce p53, subsequently promoting apoptosis [27]. Increased ROS levels were also associated with mitochondrial iron overload, which leads to cardiomyocyte ferroptosis [28]. This is a non-apoptotic process of programmed death, which uses increased levels of lipid peroxidation [29]. Ferroptosis leads to the increased aperture of the mitochondrial permeability transition pore, which releases more Ca_{2+} and cytochrome C, leading to increased apoptosis [30,31].

Another well-cited mechanism proposed is alterations to gene expression, specifically the downregulation of actin, desmin, troponin, and myosin, both light and heavy chains proteins [32]. Losing these proteins reduces healthy myofibrils involved in myocardial contraction [33]. Many other changes in gene expressions are attributed to DIC, such as the downregulation of sarcoplasmic reticular ATPase, which leads to altered myocardial diastolic function [34]. Another note-worthy pathological mechanism well-cited in DIC is mitochondrial metabolic derangements. Cardiac downregulation of PPAR transcription factors that transcribe genes that regulate metabolism in mitochondria was displayed in doxorubicin patients [35].

Epidemiology and Risk Factors

Doxorubicin-induced cardiomyopathy (DIC) is considered a significant concern of chemotherapy. In a study evaluating

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doxorubicin-induced cardiomyopathy among patients with soft tissue sarcoma, the incidence of DIC was 46%. Cardiac function of patients younger than 40 remained stable; however, left ventricular function deteriorated in patients older than 40. Gender, tumor location, and radiation treatment were not associated with the risk of doxorubicin-induced cardiomyopathy in this study [36]. Cardiac complications arise in almost 10% of cases of doxorubicin therapy [37]. The risk of doxorubicin-induced heart failure may increase with a cumulative dose. The maximal standard cumulative dose for Doxorubicin is 400-450 mg/m, with a heart failure prevalence of almost 5% [38]. The incidence of doxorubicin-induced cardiomyopathy varies as some patients develop subclinical cardiac dysfunction [39]. Doxorubicin is an antitumor medication that is used to treat breast cancer, lymphoma, leukemia, sarcoma, and other solid tumors. Several risk factors can be associated with anthracycline-induced cardiotoxicity. These include female, age (>65 years, <18 years), radiation therapy involving the heart, and concomitant cardiotoxic chemotherapies. Doxorubicin-induced cardiomyopathy (DIC) is considered a significant concern of chemotherapy. In a study evaluating doxorubicin-induced cardiomyopathy among patients with soft tissue sarcoma, the incidence of DIC was 46%. Cardiac function of patients younger than 40 remained stable; however, left ventricular function deteriorated in patients older than 40. Gender, tumor location, and radiation treatment were not associated with the risk of doxorubicin-induced cardiomyopathy in this study [36]. Cardiac complications arise in almost 10% of cases of doxorubicin therapy [37].

The risk of doxorubicin-induced heart failure may increase with cumulative dose. The maximal standard cumulative dose for Doxorubicin is 400-450 mg/m, with a heart failure prevalence of almost 5% [38]. The incidence of doxorubicin-induced cardiomyopathy varies as some patients develop subclinical cardiac dysfunction [39]. Doxorubicin is an antitumor medication that is used to treat breast cancer, lymphoma, leukemia, sarcoma, and other solid tumors. Several risk factors can be associated with anthracycline-induced cardiotoxicity. These include female, age (>65 years, <18 years), radiation therapy involving the heart, and concomitant cardiotoxic chemotherapies. Also, pre-existing cardiovascular risk factors such as smoking, hypertension, diabetes mellitus, and coronary artery disease can potentiate adverse effects on the heart [38].

Various strategies, such as antioxidants and pharmacological treatment, have been discussed to prevent the damaging cardiac effects of Doxorubicin. Several risk factors have been identified to trigger these events. These include free radical-induced myocardial injury, lipid peroxidation, and mitochondrial damage [37,38,40]. The roles of systemic inflammation, endothelial injury, and neutrophil recruitment have been discussed as mechanisms leading to DIC [41]. Bitral et al. [42] also highlighted risk factors such as advanced age, pre-existing heart disease, and high cumulative doses of Doxorubicin [42]. It has been stated in the scientific literature that genetics plays an essential role in the susceptibility to doxorubicin-induced cardiotoxicity. Dystrophin deficiency has been highlighted as a genetic factor that increases susceptibility to doxorubicin-induced cardiotoxicity. Deng et al. emphasized in their paper that alterations in genes encoding cardiac cytoskeleton or sarcolemma proteins may increase susceptibility to doxorubicin-induced cardiotoxicity [43]. The most discussed cardiotoxic effect of Doxorubicin is left ventricular dysfunction. Anghel et al. stated that Doxorubicin exerted proper ventricular toxic effects at the same time as those reported in the left ventricle, and these effects should be considered as a sequel of mitochondrial dysfunction [39,44].

Clinical Presentation and Diagnosis

Doxorubicin cardiotoxicity is categorized as acute or chronic based on onset, with acute cardiotoxicity having an incidence of approximately 11% and chronic cardiotoxicity about 1.7%, often manifesting within 30 days or after a latency period of 6 to 10 years [45]. Acute Doxorubicin-induced cardiotoxicity starts within 24 hrs. of the infusion and includes ECG (electrocardiogram) abnormalities such as atypical ST-T changes, reduced QRS voltages, sinus tachycardia, premature supraventricular and ventricular complexes, QT interval prolongation, and, rarely, acute myocardial ischemia. These electrocardiographic changes are usually associated with few symptoms or asymptomatic [46]. The cardiotoxicity is related to the total cumulative dose administered, as well as to acute peak levels, age at exposure, and the concurrent administration of other cardiotoxic antineoplastic agents [47]. It was estimated that approximately 26% of patients progressed to heart failure when receiving DOX at a cumulative dose of over 550 mg/m^2 [48]. The clinical manifestations included fatigue, sinus tachycardia, tachypnea, cardiac enlargement, edema, pulmonary edema, hepatomegaly, and pleurisy, all of which are common to congestive heart failure with other causes. Associated arrhythmias included ventricular tachycardia or fibrillation, heart block, and occasionally sudden death [47]. DOX-treated patients exhibit extensive cardiac remodeling, resulting in vast cytoplasmic vacuolization, sarcoplasmic reticulum swelling, and myofibrillary disarray [49].

The diagnosis of doxorubicin cardiomyopathy should consist of a complete examination of the cardiovascular system to detect the presence of signs of overt heart failure. An ECG should also be obtained, which usually demonstrates nonspecific ST-T wave changes. A chest X-ray is also helpful to assess cardiomegaly and signs of pulmonary venous congestion. Impaired glucose and fatty acid metabolism have been observed in DOX cardiomyopathy [50]. Neurohormone and cardiac enzyme measurements, plasma B-type natriuretic peptide levels, and troponin T or I levels are also used for diagnosis [51]. Radionuclide angiography to measure left ventricular ejection fraction has been the most popular method for monitoring patients receiving DOX. In addition, serial

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echocardiographic measurement of ejection fraction is also a sensitive, noninvasive tool for primary detection and follow-up of DOX-induced cardiomyopathy [47].

The golden standard is endomyocardial biopsy of the right ventricle because of its high sensitivity and specificity. Endomyocardial tissue from the right ventricle will show typical histopathological changes, including cytoplasm vacuolization [46]. Antimyosin antibody studies and endomyocardial biopsies may be employed, with the latter showing characteristic features of doxorubicin cardiomyopathy [51]. MIBG (metaiodobenzylguanidine) nuclear imaging can be employed to assess cardiac adrenergic denervation, analysis of cardiac accumulation, and washout of radiolabeled MIBG could become a powerful tool for detecting early-stage cardiomyopathy [47]. Cardiac magnetic resonance imaging can also be used to assess LV systolic function. Annexin V has been used to detect apoptosis induced by doxorubicin [50].

Prevention Strategies

Doxorubicin-induced cardiomyopathy (DIC) poses a significant challenge in cancer treatment, necessitating strategies to mitigate its cardiotoxic effects. Limiting doxorubicin dosage has been a primary approach [52]. A review has shown that DIC depends on dose administration such that <400 mg/m2 is less toxic, while > 400 mg/m2 is toxic. However, cardiac pathophysiology and cell death can occur from stress activating c-Jun N-terminal kinases (JNKs) and cellular stress on p38-MAPKs [52]. Adjunct cardioprotective agents such as Dexrazoxane, an iron chelator, demonstrated cardioprotective effects in patients receiving doxorubicin [52]. Furthermore, alternative chemotherapy regimens have been explored to minimize cardiotoxicity while maintaining antitumor efficacy. Studies suggested anthracycline-free regimens such as taxanes or targeted therapies in patients with high cardiomyopathy risk [53]. Nonetheless, liposomal formulations of doxorubicin have shown reduced cardiotoxicity compared to conventional formulations [54]. These approaches underscore the multidimensional approaches needed to mitigate DIC, emphasizing dose optimization, adjunctive cardioprotective agents, and alternative chemotherapy regimens.

Cardiac surveillance and monitoring protocols prevent DIC, particularly in high-risk patients. Regular cardiac assessments facilitate early detection of myocardial damage, enabling timely intervention to mitigate cardiotoxicity and improve patient outcomes [55]. Echocardiography, cardiac magnetic resonance imaging (MRI), and cardiac biomarkers are integral to monitoring protocols. For instance, echocardiographic parameters like left ventricular ejection fraction (LVEF) serve as early indicators of cardiac dysfunction, prompting intervention if declines are detected [55]. Similarly, cardiac MRI provides a detailed assessment of cardiac structure and function, aiding in the early detection of subclinical cardiotoxicity [55].

Furthermore, cardiac biomarkers such as troponin and brain natriuretic peptide (BNP) levels reveal the extent of myocardial injury and hemodynamic stress, guiding therapeutic decisions. In fact, close monitoring allows for personalized management strategies tailored to individual patient needs; dose adjustments, adjunctive cardioprotective agents like Dexrazoxane, or alternative chemotherapy regimens may be considered to minimize further cardiac damage [52,56-57]. In essence, cardiac surveillance and monitoring protocols serve as crucial tools in the proactive management of doxorubicin-induced cardiomyopathy, enabling early intervention and optimization of therapeutic strategies in high-risk patients.

Management of Doxorubicin-Induced Cardiomyopathy

The management of Doxorubicin-Induced Cardiomyopathy (DIC) poses a significant challenge due to its progressive nature and potential for irreversible cardiac damage. Current treatment strategies for established DIC primarily focus on mitigating cardiac dysfunction and alleviating symptoms. Pharmacological interventions play a central role in the management of DIC, with agents such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and angiotensin II receptor blockers (ARBs) demonstrating efficacy in preserving cardiac function and preventing further deterioration [58,59]. These medications target various pathways involved in the pathogenesis of DIC, including inhibition of renin-angiotensin-aldosterone system activation, attenuation of sympathetic nervous system activity, and reduction of myocardial fibrosis. Additionally, mineralocorticoid receptor antagonists, such as spironolactone, have shown promise in improving outcomes and reducing mortality in patients with DIC [60]. However, it is essential to monitor patients closely for potential adverse effects, such as hypotension, hyperkalemia, and renal dysfunction, particularly in those with pre-existing comorbidities.

In addition to pharmacotherapy, non-pharmacological approaches play a crucial role in managing DIC, aiming to optimize cardiac function and improve patients' quality of life. Lifestyle modifications, including dietary changes, regular exercise, and smoking cessation, are integral components of comprehensive management strategies for DIC [61]. Patients with DIC should also receive education and counseling regarding medication adherence, symptom recognition, and adherence to recommended follow-up appointments to monitor disease progression and treatment response. Furthermore, cardiac rehabilitation programs offer structured exercise training, education, and psychosocial support, helping patients regain functional capacity and reduce cardiovascular risk factors [62]. Advanced heart failure therapies, such as cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillator (ICD) placement, may be considered in select cases to optimize cardiac function and reduce the risk of arrhythmias and sudden cardiac death [63].

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Supportive therapies are vital in alleviating symptoms and improving cardiac function in patients with DIC. Symptomatic management aims to address heart failure symptoms, such as dyspnea, fatigue, and fluid retention, through diuretic therapy and sodium restriction [64]. Regularly monitoring fluid status, electrolyte levels, and renal function is essential to prevent complications associated with diuretic therapy, such as electrolyte imbalances and worsening renal function. Furthermore, nutritional support and supplementation with antioxidants, such as coenzyme Q10 and vitamin E, may mitigate oxidative stress and preserve cardiac function in patients with DIC [65]. Psychological support and counseling are also integral components of supportive care, helping patients cope with DIC's emotional and psychological impact and promoting adherence to treatment recommendations [66].

Future Directions and Novel Therapies

Despite extensive research on anthracycline-related cardiotoxicity, treatment options remain limited. Dexrazoxane is the only drug approved by the FDA for preventing doxorubicin-induced cardiotoxicity [67]. However, its use is restricted due to its potential impact on tumor response rates and risk of secondary malignancies [68]. Given the widespread use of doxorubicin in chemotherapy, there is a pressing need for alternative prevention strategies. Current research shows promising results, primarily targeting mitochondrial dysfunction, a major hallmark of doxorubicin-related cardiotoxicity. Various small molecules under development have shown promise in preserving mitochondrial function, reducing oxidative stress, and protecting against cardiac injury in both in vitro and in vivo studies. Examples include DMX-5804, liensinine, melatonin, metformin, dexmedetomidine, phenylalanine-butyramide, nicotinamide riboside, and berberine [69-75]. The latter two are believed to enhance autolysosome clearance via NAD+/SIRT1 signaling, thereby reducing cardiac injury and myocardial dysfunction in Doxorubicin-treated mice [76]. Despite encouraging preclinical data, clinical trials have yielded disappointing results, possibly due to factors such as species-specific differences, inadequate sample sizes, and heterogeneity in anthracycline doses and cancer types [77-79].

Consequently, the efficacy of antioxidant therapy remains uncertain and requires further investigation. A novel approach involves targeting antioxidants specifically to mitochondria, where they are most needed [80]. Mitochondria-targeted antioxidants like mitoQ and mitoTempo have been developed for this purpose [79,81]. Additionally, research is exploring the use of exogenous mitochondria through stem cell transplantation as a potential therapeutic avenue [82]. In biomarkers for cancer treatment-related cardiac damage, troponin and myeloperoxidase are prominent candidates [83]. Troponin elevation before cardiac symptoms manifest indicates subclinical myocardial damage and is associated with increased mortality in cancer patients [84]. Arginine–nitric oxide metabolites are also being investigated as potential biomarkers due to their role in endothelial dysfunction and oxidative stress associated with anthracycline-induced cardiac damage [85]. Levels of these metabolites were found to increase significantly shortly after chemotherapy administration [86].

Conclusion

Doxorubicin-induced cardiomyopathy (DIC) remains a significant concern in cancer treatment due to its potential for irreversible cardiac damage and adverse impact on patient outcomes. Despite advances in understanding its mechanisms and risk factors, effective prevention and management strategies are still lacking. Current approaches primarily focus on limiting doxorubicin dosage, adjunctive cardioprotective agents, and alternative chemotherapy regimens to minimize cardiotoxicity. However, these strategies have limitations and may not be sufficient to mitigate DIC to the fullest extent. Future research directions aim to develop novel therapies targeting mitochondrial dysfunction, oxidative stress, and myocardial injury to improve patient outcomes. Additionally, advances in biomarker discovery hold promise for early detection and monitoring of DIC, facilitating timely intervention and personalized management strategies.

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