Beyond Chemotherapy: Tackling Doxorubicin-Induced Cardiotoxicity Through Innovative Management and Future Therapies

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Abstract

Doxorubicin, a widely used anthracycline chemotherapeutic agent, has significantly improved cancer survival rates but is notably limited by its potential to cause dose-dependent cardiotoxicity. This review highlights the molecular mechanisms, risk factors, preventive measures, monitoring approaches, and management strategies for doxorubicin-induced cardiotoxicity. Advances in liposomal formulations, dexrazoxane, antioxidants, and stem cell-based therapies are discussed alongside emerging approaches such as nanotechnology-driven drug delivery systems and biomarker discovery. The integration of preventive strategies with personalized medicine is expected to minimize cardiotoxic risks while preserving therapeutic efficacy.

Keywords: Doxorubicin, cardiotoxicity, biomarkers, preventive strategies, chemotherapy

INTRODUCTION

Doxorubicin (DOX), an anthracycline antibiotic discovered in the 1960s, remains one of the most effective chemotherapeutic agents against a wide spectrum of malignancies, including breast, ovarian, bladder, thyroid, leukemias, and sarcomas [1,2]. Its antitumor effect is mediated through DNA intercalation, inhibition of topoisomerase II, and free radical generation, ultimately leading to apoptosis of rapidly dividing cancer cells [1]. Despite its therapeutic value, the clinical utility of doxorubicin is restricted by dose-dependent cardiotoxicity, a complication that can manifest as left ventricular dysfunction, arrhythmias, or heart failure [2,11].

The underlying mechanisms of doxorubicin-induced cardiotoxicity are multifactorial. Excessive production of reactive oxygen species, mitochondrial damage, calcium dysregulation, and topoisomerase IIβ–mediated DNA injury are considered central pathways leading to cardiomyocyte death [11,13]. Importantly, cardiotoxicity may occur during treatment or present years later, contributing to long-term morbidity in cancer survivors [14,15].

Given the rising population of cancer survivors, reducing doxorubicin cardiotoxicity has become a major clinical priority. Advances such as liposomal drug formulations [3], cardioprotective agents like dexrazoxane [4,5], antioxidants [6–10], and dose modifications have shown promising results. Furthermore, emerging strategies including biomarkers [12,21–24], nanotechnology-based delivery systems [25,26], and stem cell–based therapies [18,19] hold potential for improving safety while preserving efficacy.
This review provides an updated overview of the risk factors, preventive strategies, monitoring tools, management approaches, and future directions in addressing doxorubicin-induced cardiotoxicity.

2. Mechanisms of Doxorubicin-Induced Cardiotoxicity

The cardiotoxicity of doxorubicin (DOX) arises from a complex interplay of molecular and cellular mechanisms, leading to progressive myocardial damage and heart failure.

- Oxidative Stress and Iron Interaction
  DOX undergoes redox cycling and interacts with iron to generate excessive reactive oxygen species (ROS). These free radicals promote lipid peroxidation, protein oxidation, and DNA strand breaks, resulting in irreversible cardiomyocyte damage [1,11]. Cardiac tissue is particularly vulnerable due to its relatively low antioxidant capacity compared to other organs [6–8].

- Mitochondrial Dysfunction
  DOX has a strong affinity for cardiolipin in the inner mitochondrial membrane, leading to mitochondrial accumulation. This disrupts the electron transport chain, decreases ATP synthesis, and causes mitochondrial DNA damage [11,13]. Chronic mitochondrial impairment contributes to energy deficit, contractile dysfunction, and apoptosis.

- Calcium Dysregulation
  By altering sarcoplasmic and endoplasmic reticulum function, DOX impairs calcium homeostasis. Abnormal calcium cycling interferes with excitation–contraction coupling, activates calpain and caspase pathways, and promotes cardiomyocyte apoptosis [11,13].

- Topoisomerase IIβ–Mediated DNA Damage
  In cardiomyocytes, DOX targets topoisomerase IIβ, causing double-strand DNA breaks and maladaptive gene expression. This pathway is now recognized as a major

contributor to chronic cardiotoxicity [11]. Dexrazoxane, a cardioprotective agent, acts in part by inhibiting this interaction [4,5].

- Apoptosis, Autophagy, and Cellular Senescence
  DOX triggers caspase-3 activation, inhibits protective autophagy, and accelerates cardiomyocyte senescence, particularly in long-term survivors [14,15]. These processes collectively reduce cardiomyocyte viability and impair tissue repair.

- Epigenetic and Structural Alterations
  Epigenetic modifications, extracellular matrix remodeling, and persistent inflammatory signaling further exacerbate cardiac injury, promoting fibrosis and left ventricular dysfunction [12,21].

3.Management of Established Cardiotoxicity

Doxorubicin-induced cardiotoxicity (DIC) presents a major clinical challenge as it may progress to irreversible cardiac dysfunction if not recognized and treated promptly. Management requires a multidisciplinary approach, integrating modifications in chemotherapy regimens, pharmacological cardioprotection, early diagnostic tools, and emerging regenerative therapies.

3.1. Liposomal formulations

The use of liposomal and pegylated liposomal doxorubicin represents a cornerstone in minimizing ongoing cardiotoxicity. These formulations encapsulate doxorubicin within lipid vesicles, thereby limiting free drug exposure to cardiac tissue while enhancing tumor uptake through the enhanced permeability and retention (EPR) effect. Clinical studies in breast and ovarian cancer patients have demonstrated a markedly lower incidence of left ventricular dysfunction compared with conventional doxorubicin, even at higher cumulative doses [3]. For patients who have already developed early cardiac impairment, switching to liposomal formulations can reduce further injury while maintaining therapeutic efficacy.

3.2. Dexrazoxane

Dexrazoxane is the most extensively studied pharmacological cardioprotective agent and remains the only FDA-approved drug for anthracycline cardiotoxicity. In addition to its iron-chelating properties, it interferes with the binding of doxorubicin to topoisomerase IIβ in cardiomyocytes, thus preventing DNA double-strand breaks [4,5]. In patients with symptomatic or asymptomatic left ventricular dysfunction, dexrazoxane may stabilize cardiac function when continued chemotherapy is unavoidable. However, its use is typically reserved for high-risk individuals due to historical concerns about secondary malignancies, although recent evidence suggests these risks are minimal [5].

3.3 Antioxidants and natural products

As oxidative stress plays a pivotal role in DIC, antioxidants have been explored both as preventive and therapeutic options. Coenzyme Q10 supplementation has shown cardioprotective benefits in preclinical and small-scale clinical studies by improving mitochondrial function and reducing oxidative stress markers [6]. Herbal extracts such as Murraya koenigii [7], ginsenosides [9], and Schinus terebinthifolius [10] demonstrated reductions in cardiac biomarkers and improvements in myocardial histology in animal models. Although not yet part of standard care, these agents may serve as adjunctive therapies in patients with established cardiotoxicity to limit progression of myocardial injury.

3.4. Dose modifications

Careful modulation of anthracycline dosing remains central to management. In patients who exhibit early signs of cardiotoxicity, dose reduction, prolonged infusion schedules, or discontinuation of doxorubicin are recommended [1,2]. Continuous infusion instead of bolus dosing lowers plasma peak concentrations, reducing myocardial exposure. Alternative regimens that combine lower-dose anthracyclines with non-cardiotoxic agents (e.g., taxanes or targeted therapies) may be considered to maintain oncologic efficacy while minimizing further cardiac damage.

3.5. Biomarkers (troponin, BNP, miRNAs)

Biomarkers play a crucial role not only in early detection but also in guiding management. Cardiac troponins (I and T) and natriuretic peptides (BNP, NT-proBNP) rise early in cardiotoxicity and are useful for identifying patients requiring intervention [12,23,24]. Novel circulating microRNAs such as iR-1 and miR-133 show promise as more sensitive and specific markers of subclinical cardiac injury [21,22]. Regular biomarker monitoring allows timely initiation of cardioprotective drugs before irreversible damage occurs.

3.6. Imaging and echocardiography

Echocardiography remains the mainstay for diagnosing and monitoring DIC, with left ventricular ejection fraction (LVEF) as the primary measure. However, advanced modalities such as global longitudinal strain (GLS) provide earlier detection of subtle myocardial dysfunction [20]. Cardiac MRI offers superior accuracy in assessing ventricular remodeling and fibrosis, making it valuable in patients with equivocal echocardiographic findings. Incorporating imaging alongside biomarker surveillance ensures comprehensive management.

3.7. Long-term follow-up in survivors

Late-onset cardiomyopathy may manifest years or even decades after anthracycline exposure, particularly in childhood cancer survivors [14,20]. Therefore, structured long-term follow-up is essential. Guidelines recommend regular echocardiographic evaluation and biomarker

testing, especially in high-risk groups such as younger patients, females, and those with cardiovascular comorbidities. Lifestyle interventions—including exercise, dietary modification, and strict blood pressure control—further reduce long-term cardiac risk.

3.8. Heart failure drugs (beta-blockers, ACE inhibitors, ARBs)

Conventional heart failure therapy plays a critical role in treating established DIC. Beta-blockers and ACE inhibitors/ARBs have been shown to preserve LVEF and reduce the risk of symptomatic heart failure [16,17]. Early initiation, even in asymptomatic patients with mild ventricular dysfunction, can attenuate progression. Clinical studies also suggest a potential survival benefit in breast cancer patients receiving anthracyclines and trastuzumab when cardioprotective drugs are used prophylactically [16]. Despite some conflicting results, they remain the standard of care for patients with anthracycline-induced cardiomyopathy.

3.9. Stem cell therapy

Emerging regenerative therapies such as mesenchymal stem cell (MSC) transplantation have shown promise in reversing established cardiotoxicity. MSCs secrete angiogenic and anti-fibrotic factors, reduce oxidative stress, and promote myocardial repair [18]. Similarly, human amniotic fluid–derived stem cell secretome has been demonstrated to attenuate doxorubicin-induced apoptosis and senescence in cardiomyocytes [19]. Although still experimental, stem cell therapy may represent a future option for patients with refractory heart failure due to DIC.

3.10. Less cardiotoxic anthracycline analogues

Alternative anthracycline analogues such as epirubicin and idarubicin were developed to reduce cardiotoxicity, though results remain mixed. Liposomal anthracyclines currently offer the best balance of efficacy and safety [3]. Ongoing research into novel anthracycline derivatives and targeted delivery systems aims to retain anticancer potency while reducing myocardial toxicity.

OVERALL SUMMARY :

Strategy	Mechanism of Action / Role	Clinical Status	References
Liposomal formulations	↓ Cardiac exposure, ↑ tumor uptake (EPR effect)	Clinical use	[3]
Dexrazoxane	Iron chelation, TopoIIβ inhibition	FDA-approved	[4,5]
Antioxidants/natural products	ROS scavenging, mitochondrial protection	Preclinical/early clinical	[6–10]

Dose modifications	↓ cumulative exposure, continuous infusion	Clinical practice	[1,2]
Biomarkers (troponin, BNP, miRNAs)	Early detection, monitoring	Clinical/experimental	[12,21–24]
Imaging (ECHO, GLS, MRI)	Functional & structural cardiac monitoring	Clinical use	[20]
Heart failure drugs (β-blockers, ACEi/ARBs)	Preserve EF, ↓ HF risk	Clinical guidelines	[16,17]
Stem cell therapy	Regeneration, paracrine effects	Experimental	[18,19]
Less cardiotoxic analogues	Epirubicin, idarubicin, liposomal forms	Clinical options	[3]

4.Future Prospects

4.1. Biomarkers for early detection

Noncoding RNAs, particularly circulating microRNAs (miRNAs), have emerged as promising biomarkers for early detection of doxorubicin-induced cardiotoxicity. Among them, miR-1 and miR-133 have demonstrated potential in identifying subclinical cardiac dysfunction before conventional imaging changes occur [21,22]. Exosomes carrying cardiac-specific RNAs and proteins have also been proposed as novel biomarkers and mediators of cardiotoxicity [21]. In addition, plasma cytokines and chemokines have been shown to correlate with abnormal left ventricular ejection fraction (LVEF) decline in patients undergoing anthracycline therapy [23]. Traditional markers such as cardiac troponins and natriuretic peptides (BNP, NT-proBNP) remain valuable for clinical monitoring, but their predictive sensitivity is limited [24]. Therefore, combining classical markers with emerging molecular biomarkers may provide greater accuracy for early diagnosis.

4.2. Nanotechnology-based drug delivery systems

Nanotechnology offers innovative strategies to minimize doxorubicin cardiotoxicity while enhancing its therapeutic efficacy. Liposomes, polymeric nanoparticles, micelles, and solid lipid nanoparticles are among the most widely studied carriers. These nanocarriers enable targeted delivery to tumors, sustained drug release, and reduced systemic exposure, thereby lowering cardiac accumulation [25,26]. Moreover, advanced nanotheranostic platforms integrate both diagnostic and therapeutic functions, allowing real-time monitoring of drug distribution and cardiac safety. By overcoming drug resistance mechanisms such as P-glycoprotein efflux, nanocarriers also improve intracellular doxorubicin concentration in tumor cells [26].

4.3. Translational and regenerative approaches

Precision medicine approaches, including pharmacogenomics and patient-derived cardiomyocyte models, may help identify patients at higher genetic risk of anthracycline cardiotoxicity and guide individualized dosing or cardioprotective interventions [23,24]. Furthermore, cell-based and exosome-derived therapies hold promise for repairing established injury. Preclinical studies using mesenchymal stem cells and their secretome have demonstrated reduced apoptosis, fibrosis, and improved myocardial function following doxorubicin injury [18,19].

Conclusion

Doxorubicin remains a cornerstone in cancer chemotherapy due to its broad-spectrum antitumor efficacy. However, its clinical use is limited by dose-dependent cardiotoxicity, which may manifest acutely during treatment or years later as progressive heart failure. The pathogenesis is multifactorial, involving oxidative stress, mitochondrial dysfunction, calcium dysregulation, topoisomerase IIβ–mediated DNA damage, and apoptotic signalling.

Effective management requires a multidisciplinary approach, integrating oncology, cardiology, and pharmacology expertise. Current strategies such as liposomal formulations, dexrazoxane, antioxidants, dose modifications, biomarker surveillance, and imaging-based monitoring form the backbone of cardio protection. For patients with established cardiotoxicity, standard heart failure therapy, long-term follow-up, and in select cases, regenerative therapies provide opportunities to mitigate adverse outcomes.

Looking forward, future directions include the validation of novel biomarkers (e.g., microRNAs, exosomes, cytokine panels) for early detection, the development of nanotechnology-based drug delivery platforms to enhance tumor targeting while reducing off-target toxicity, and the application of regenerative therapies such as stem cell–derived exosomes. Integration of precision medicine and pharmacogenomics will further enable individualized risk stratification and tailored interventions.

In conclusion, balancing the anticancer efficacy of doxorubicin with strategies to minimize cardiotoxicity is essential to improving the long-term quality of life and survival of cancer patients. A proactive, multidisciplinary, and innovation-driven approach will be central to advancing cardio-oncology care.

Acknowledgments

The authors sincerely thank RVS College of Pharmaceutical Sciences for their continuous support and encouragement throughout the preparation of this manuscript.

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