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Cardiotoxicity of Anticancer Treatments in Children: A Literature Review

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Abstract | **Review Article**

Advances in pediatric oncology have significantly improved survival rates, exceeding 80% for certain malignancies, but have led to an increased risk of late cardiovascular complications. This comprehensive literature review examines the mechanisms, risk factors, baseline evaluation, long-term follow-up, and cardioprotective strategies based on recent evidence, emphasizing the need for multidisciplinary management to optimize outcomes for survivors.

Keywords: Cardio-Oncology, Childhood Cancer Survivors, Cardiotoxicity, Late Cardiovascular Complications, Pediatric Oncology.

INTRODUCTION

Therapeutic advancements in pediatric oncology have transformed the prognosis of childhood cancers, achieving survival rates above 80% for certain leukemias and solid tumors. However, this success comes with a significant rise in late cardiovascular complications, including heart failure, dilated or restrictive cardiomyopathies, premature coronary artery disease, valvular and pericardial diseases, and arrhythmias. Epidemiological data, such as those from the Childhood Cancer Survivor Study, indicate that the cumulative incidence of these cardiac morbidities continues to rise up to 30 years post-diagnosis, with a fivefold increased risk of cardiovascular mortality compared to the age- and sex-matched general population [1,4].

These cardiac complications are often clinically silent for years or even decades, posing challenges for early detection. This latency underscores the critical need for structured, lifelong cardiovascular follow-up tailored to each patient's risk profile. Guidelines from the European Society of Cardiology (ESC), in collaboration with the European Hematology Association (EHA) and the International Cardio-Oncology Society (ICOS), as well as the Children's Oncology Group (COG) and the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG), provide frameworks for this follow-up, emphasizing early detection of subclinical cardiac damage using advanced echocardiography, cardiac biomarkers, and magnetic resonance imaging (MRI) [2,3,32-34]. The ultimate goal is to identify these abnormalities at a reversible stage and implement appropriate cardioprotective interventions to prevent progression to severe heart failure.

This review aims to synthesize current knowledge on cardiotoxicity in pediatric oncology. We will first define and classify cardiotoxicity, then identify intrinsic and treatment-related risk factors. Next, we will detail the molecular and cellular mechanisms for each major therapeutic class. We will also discuss baseline evaluation and risk stratification, long-term follow-up (including in pregnant survivors), and cardioprotective strategies, ranging from pharmacological agents to optimized treatment delivery. This review draws on an in-depth analysis of recent clinical studies, systematic reviews, and international guidelines to provide a comprehensive and actionable perspective for clinicians managing these vulnerable patients.

Definitions and Nosology of Cardiotoxicity

Cancer therapy-related cardiac dysfunction (CTRCD) encompasses a broad spectrum of cardiac pathologies induced by anticancer agents. It is classified into two main profiles: symptomatic CTRCD, characterized by overt heart failure symptoms such as dyspnea, lower limb edema, severe fatigue, and potentially cardiogenic shock in severe cases; and asymptomatic CTRCD, defined by biomarker elevations (troponin I or T, BNP, or NT-proBNP), a global longitudinal strain (GLS) reduction >15% from baseline,

or impaired left ventricular ejection fraction (LVEF) without clinical symptoms [4,5].

The phenotypes of cardiotoxicity are diverse and often tied to the specific treatment. Common manifestations include left ventricular systolic dysfunction (reduced contractility), diastolic dysfunction (impaired relaxation), restrictive cardiomyopathy (due to myocardial fibrosis), and myocarditis, particularly associated with immunotherapies like immune checkpoint inhibitors (ICIs). Premature coronary artery disease with accelerated atherosclerosis is frequent after thoracic radiotherapy, while valvular (leaflet thickening, fibrosis, calcifications leading to regurgitation or stenosis) and pericardial (constrictive pericarditis) complications are also well-documented, often secondary to radiation [5,22-26]. Arrhythmias (supraventricular or ventricular) and conduction abnormalities (atrioventricular blocks) complete this nosological spectrum. These entities may coexist and progress gradually, highlighting the importance of precise classification to guide clinical management.

Risk Factors for Cardiotoxicity

Cardiotoxicity risk factors in pediatric oncology are categorized into patient-related (intrinsic) and treatment-related (extrinsic) factors, enabling personalized risk stratification critical for tailored follow-up and preventive measures.

1. Patient-Related Factors

Individual susceptibility is heavily influenced by age at treatment exposure. Children under 3 years exhibit reduced doxorubicin clearance, correlated with age, increasing exposure to toxic metabolites [6]. The limited regenerative capacity of cardiomyocytes in young children necessitates adaptive hypertrophy of surviving cells to maintain cardiac output, but this compensation is inadequate long-term, leading to progressive heart failure as the body grows [3]. Gender disparities are notable: although girls have a higher likelihood of overall clinical cure, they are more susceptible to severe cardiotoxicity [7]. Murine studies have elucidated the cardioprotective role of androgens via PI3K, AKT, and NOS-3 signaling pathways, explaining why androgen receptor knockout mice show greater left ventricular dysfunction post-doxorubicin [8].

Conventional cardiovascular risk factors (hypertension, diabetes, dyslipidemia) are rare in young survivors but increase significantly after age 40 without plateauing, necessitating dynamic follow-up adjustments [6]. Genetic polymorphisms, such as those in RARG, UGT1A6, and CBR3 genes, promote the accumulation of toxic anthracycline metabolites, heightening vulnerability [9]. Preexisting congenital heart diseases further amplify risk by rendering the myocardium more susceptible to therapeutic insults.

2. Treatment-Related Factors

Anthracyclines (e.g., doxorubicin, daunorubicin) pose a dose-dependent risk, with toxicity increasing at cumulative doses >250 mg/m², influenced by administration mode (bolus vs. prolonged infusion) and formulation (liposomal vs. conventional) [10,11]. Genetic factors modulate this sensitivity [1]. Thoracic radiotherapy risk depends on total dose, mean heart dose, irradiated cardiac volume, fractionation schedule, and technique (IMRT or proton therapy reducing risk); mediastinal or left hemithorax fields are particularly high-risk [12,13].

Therapeutic combinations potentiate effects: anthracyclines with trastuzumab exert synergistic cardiotoxicity, tyrosine kinase inhibitors or anti-VEGF agents promote hypertension and ischemia, and immunotherapies induce myocarditis [14,15]. Bone marrow transplantation with total body irradiation (TBI) adds microvascular damage, diffuse ischemia, and metabolic alterations (hypertension, diabetes, dyslipidemia) [16]. A thorough understanding of these factors enables risk anticipation and mitigation from the treatment planning stage.

Mechanisms of Cardiotoxicity

Cardiotoxicity mechanisms vary by therapeutic agent but often involve oxidative stress, DNA damage, and chronic inflammation. We detail these by class.

1. Anthracyclines

Agents like doxorubicin induce multifactorial cardiotoxicity. The primary mechanism is the formation of a stabilized topoisomerase IIβ-DNA complex, causing double-strand DNA breaks and cardiomyocyte apoptosis [17,18]. Iron chelation promotes reactive oxygen species (ROS) generation, leading to lipid peroxidation, contractile protein damage, and mitochondrial dysfunction with fragmentation, respiratory chain disruption, and reduced ATP levels [19,20]. Sarcomeric and calcium metabolism alterations disrupt myofibrillar organization and excitation-contraction coupling [21]. A dose-effect relationship is established, with significant risk >250 mg/m² and high risk >400-550 mg/m² (doxorubicin equivalents) [10,11]. Temporality varies: acute (rare, during treatment), early (within a year), or late (years post-treatment), progressing to dilated cardiomyopathy [19]. Figure 1 illustrates these pathways: topoisomerase-DNA complex, transcriptional inhibition, ROS via multiple pathways, mitochondrial dysfunction, and calcium flux inhibition by doxorubicinol [14].

2. Thoracic Radiotherapy

Radiotherapy damages multiple cardiac structures. In coronaries, it accelerates atherosclerosis via endothelial dysfunction (reduced nitric oxide), inflammation, and microvascular rarefaction, typically affecting the right coronary (internal mammary irradiation) or distal left anterior descending artery (left

thoracic/mammary irradiation) [22,23]. Myocardially, DNA and mitochondrial damage generate ROS, activate apoptosis, and promote a pro-inflammatory milieu driving fibroblast differentiation and collagen deposition, leading to progressive fibrosis and heart failure (reduced or preserved LVEF) [24]. Left-sided valves undergo thickening, fibrosis, and calcification, predominantly causing regurgitation [25]. Pericardial and conduction tissue fibrosis causes constriction and blocks [26]. Dose-effect >30-35 Gy or mean heart dose, with ischemic risk rising linearly per Gy; complications are mostly late (years post-exposure) [12,13]. Figure 3 depicts these mechanisms: endothelial dysfunction, inflammation, apoptosis, fibrosis [21]. Figure 4 shows the timeline from early (myocarditis) to very late (coronary disease >10 years) [26].

3. Targeted Therapies

These agents block pathways like HER2, VEGFR, or EGFR, critical for tumor proliferation but also cardiomyocyte survival. HER2 inhibition disrupts myocardial regeneration, while anti-VEGF induces endothelial dysfunction, hypertension, and ischemia [27]. Some multikinase inhibitors increase ROS, mitochondrial damage, and apoptosis. In pediatrics, their use is limited to refractory cases with molecular alterations (BRAF V600E, NTRK/ALK/ROS1, HER2), often in clinical trials [27].

4. Immunotherapies

ICIs activate T-lymphocytes, leading to autoimmune myocarditis via cross-recognition of tumor/cardiac antigens [28]. CAR-T cells trigger cytokine release syndrome (CRS) with tachycardia, hypotension, and transient myocardial failure via IL-6, IFN-γ, and TNF-α [29]. These therapies are expanding in pediatric hematologic malignancies [30].

Baseline Evaluation and Risk Stratification

Baseline evaluation aims to quantify pre-treatment risk to tailor monitoring and cardioprotection.

1. Risk Factor Identification

Includes age, sex, personal/family cardiac history, comorbidities, planned anthracycline dose, and thoracic radiotherapy [31].

2. Cardiac Function Assessment

ECG for conduction/QT abnormalities; biomarkers (BNP/NT-proBNP, troponins); echocardiography (LVEF, strain, diastolic function, right ventricle, pulmonary artery pressure); MRI if acoustic window is inadequate [32].

3. Risk Stratification

In pediatrics, an exposure-driven approach (COG/IGHG) identifies high risk for anthracyclines >250 mg/m², radiotherapy >15 Gy, targeted therapies, transplantation, or congenital heart disease [33,34]. Table 1 summarizes these criteria. The HFA-ICOS score, validated in adults, is not suitable for children [35].

Long-Term Follow-Up

Annual cardiovascular risk factor assessment is recommended. Echocardiography frequency varies: annually for high risk (COG/IGHG), every 2 years (ESC); every 2-5 years for intermediate risk; none for low risk [36-38]. Figure 5 illustrates this schedule. In high-risk female survivors, preconception multidisciplinary consultation is advised; baseline evaluation (history, ECG, biomarkers, echocardiography) is indicated, with echocardiography at the 1st trimester (12 weeks) and potentially 2nd trimester (20 weeks) for high-risk or cardiotoxic-exposed patients [39]. Figure 6 details follow-up during pregnancy under anthracyclines.

Cardioprotective Measures 1. Pharmacological Treatments

Dexrazoxane: the only approved agent, inhibits topoisomerase IIβ and chelates iron; reduces cardiac events for doses ≥250 mg/m² without compromising antitumor efficacy, despite theoretical secondary tumor risk [40-42]. Liposomal anthracyclines: lipid encapsulation targets tumors via enhanced vascular permeability, with slow-release reducing plasma peaks and cardiotoxicity; equivalent efficacy, safer profile [43-45]. Neurohormonal blockers: ACE inhibitors (enalapril) protect short-term LVEF and biomarkers but effects wane; hypotension is a concern [46-48]. Beta-blockers: carvedilol's antioxidant properties improve strain in children [49-51]. Statins: anti-inflammatory, protective in animal models; ongoing trials, potential benefit for metabolic syndrome in survivors [52,53].

2. Treatment Delivery Optimization

Prolonged infusions (>1h) vs. bolus reduce doxorubicin peaks, limiting oxidative stress without compromising efficacy; optimal duration is undetermined, with constraints like hospitalization, cost, and phlebitis [54,55].

3. Radiotherapy Optimization

Modern techniques (3D-CRT, IMRT, proton therapy) minimize cardiac volume exposure; field evolution (extended to involved-node) reduces heart dose threefold; Deep Inspiratory Breath Hold (DIBH) distances the heart via thoracic expansion [56,57]. Long-term benefits require confirmation in large, long-followed cohorts.

4. Dietary Supplements

Antioxidants (vitamins E/D/B1, coenzyme Q10, carnitine) neutralize ROS without reducing antineoplastic activity; promising in models but limited/conflicting clinical evidence necessitates further research [58-62].

CONCLUSION

Cardio-oncology follow-up for pediatric cancer survivors is a critical public health challenge, given the rising incidence of late cardiovascular sequelae. Elucidated mechanisms—from anthracycline oxidative stress to radiation-induced fibrosis—guide precise risk stratification and targeted interventions. International guidelines advocate personalized follow-up integrating advanced imaging and biomarkers to detect subclinical damage. Future directions include innovations like liposomal anthracyclines, dexrazoxane, and heart-sparing radiotherapy, alongside multidisciplinary management. Robust pediatric studies are essential to refine these strategies, aiming not only for survival but also for longevity and quality of life comparable to the general population.

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