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Cardiotoxic effects of anthracyclines – a literature review

Kardiotoksyczny wpływ antracyklin na układ sercowo-naczyniowy – przegląd

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Abstract

Adverse effects associated with cancer treatment, including cancer therapy-related cardiovascular toxicity (CTR-CVT), affect patients' quality of life and overall survival. Severe and potentially life-threatening cardiotoxicity associated with myocardial dysfunction is most likely to occur after treatment with anthracyclines, which are commonly used in cancer therapy. Cardiotoxicity is a significant complication for the patient and may also necessitate interruption of oncological treatment. The mechanism of anthracycline-induced cardiotoxicity is complex, multifactorial and not fully understood. Studies to date suggest a link between the formation of reactive oxygen species, oxidative damage and the subsequent induction of cardiac cell apoptosis. Knowledge of the mechanisms underlying anthracycline cardiotoxicity allows for safe implementation of the best possible oncological treatment in cancer patients by minimising the risk of CTR-CVT, as well as for planning preventive and monitoring interventions for the early detection and treatment of potential cardiovascular complications. Therefore, the search for effective methods to prevent anthracycline-induced cardiotoxicity and its clinical consequences, which have a negative impact on prognosis and quality of life, remains one of the major challenges faced by oncologists and cardiologists caring for cancer patients. This review discusses the main mechanisms underlying anthracycline cardiotoxicity and emphasises the need to identify an increased risk of anthracycline-induced cardiotoxicity in the context of optimising cardio-oncological management.

Keywords: anthracyclines, cardiotoxicity, cardiovascular oncology, heart diseases

Streszczenie

Działania niepożądane związane z leczeniem onkologicznym, w tym toksyczność sercowo-naczyniowa (*cancer therapy-related cardiovascular toxicity*, CTR-CVT), wpływają na jakość życia i ogólne przeżycie chorych. Najczęściej do ciężkiej i potencjalnie zagrażającej życiu kardiotoksyczności związanej z dysfunkcją mięśnia sercowego dochodzi po leczeniu antracyklinami, powszechnie stosowanymi w terapii nowotworów. Kardiotoksyczność sama w sobie jest istotnym powikłaniem, co więcej w wyniku CTR-CVT może zaistnieć konieczność przerwania leczenia onkologicznego. Mechanizm kardiotoksyczności wywołanej przez antracykliny jest złożony i wieloczynnikowy, nie w pełni poznany. Wyniki dotychczasowych badań wskazują na związek pomiędzy powstawaniem reaktywnych form tlenu, uszkodzeniem oksydacyjnym i późniejszą indukcją apoptozy w komórkach mięśnia sercowego. Znajomość mechanizmów kardiotoksyczności antracyklin umożliwia bezpieczne stosowanie najlepszego możliwego leczenia onkologicznego dzięki minimalizacji ryzyka wystąpienia CTR-CVT, jak również pozwala na określenie planów prewencji i nadzoru w celu wczesnego wykrywania oraz leczenia powikłań sercowo-naczyniowych. Stąd też jednym z ważnych wyzwań, jakie stoją przed onkologami i kardiologami zajmującymi się pacjentami z chorobą nowotworową, jest poszukiwanie skutecznych metod zapobiegania kardiotoksyczności poantracyklinowej oraz jej konsekwencjom klinicznym, które negatywnie wpływają na rokowanie i jakość życia. W pracy omówiono najważniejsze

mechanizmy kardiotoksycznego działania antracyklin, podkreślając konieczność identyfikacji indywidualnego zwiększonego ryzyka kardiotoksyczności poantracyklinowej w kontekście optymalizacji postępowania kardioonkologicznego.

Słowa kluczowe: antracykliny, kardiotoksyczność, kardioonkologia, choroby serca

INTRODUCTION

Advances in anticancer treatment have significantly improved cancer patient survival; however, the high incidence of cancer therapy-related cardiovascular toxicity (CTR-CVT) remains a major clinical concern, adversely impacting both quality of life and long-term outcomes[1,2]. The most common cardiotoxic complications associated with anticancer therapy include both asymptomatic and symptomatic cancer therapy-related cardiac dysfunction (CTRCD), as well as myocarditis, hypertension, venous and arterial thromboembolic events, cardiac arrhythmias, and QT interval prolongation[1–3]. Severe and potentially life-threatening cardiotoxicity, most commonly related to cardiac dysfunction, frequently arises from the use of anthracyclines (ACs) – cytostatics widely used for the treatment of various malignant tumours in both adults and children (including breast, endometrial, gastric, thyroid, prostate, and ovarian cancers, non-small cell lung cancer, as well as soft tissue and bone sarcomas), as well as in proliferative diseases of the lymphatic system (such as acute lymphoblastic and myeloblastic leukaemia and Hodgkin's lymphoma)[1–4].

The aim of this study was to discuss the key mechanisms underlying anthracycline-induced cardiotoxicity (AIC) and to explore the potential for identifying individuals at increased risk, with the goal of optimizing cardio-oncological management. A systematic literature review was conducted using the PubMed, Medline, Scopus, and Web of Science databases to assess the most relevant mechanisms of AIC. The search strategy included the MeSH terms: anthracyclines, cardiotoxicity, cardiovascular oncology, and heart diseases. The search was restricted to papers published in English in peer-reviewed journals and involving adult populations only. Observational studies, randomised controlled trials, review articles, systematic reviews, and guidelines issued by professional societies were included in the review.

ANTHRACYCLINE-INDUCED CARDIAC DYSFUNCTION

Cardiotoxicity

Cardiotoxicity is the primary adverse effect of anthracyclines and may limit their use in cancer therapy. Although initially subclinical, the progressive and long-term impairment of myocardial function significantly increases the risk of overt heart failure (HF)[1,2,5]. Symptomatic cardiac dysfunction resulting from anthracycline therapy is linked to a poor prognosis and may lead to death[6]. Early diagnosis of anthracycline-induced cardiac dysfunction (ACD) enables the initiation of cardioprotective therapy. In this context, close collaboration between oncologists and cardiologists during cancer treatment is essential[7].

Clinical manifestations of cardiotoxicity may appear at various time points following anticancer treatment. According to the current classification system, cardiotoxicity can be classified as early-onset or acute (during or within 2 weeks after AC treatment), early-onset chronic (within the first year of AC treatment), and late-onset chronic (several years after AC treatment initiation)[8]. The prevalence of acute AIC is approximately 11%[6,9,10]. It most commonly presents as retrosternal chest pain and palpitations due to supraventricular or ventricular arrhythmias. Electrocardiogram (ECG) findings may show nonspecific ST-segment changes and reduced QRS amplitude[1,6].

The mechanism of acute anthracycline-induced myocardial damage is not yet fully understood, although myocardial oedema appears to be the most likely cause[6,9]. Acute heart failure (AHF), while less common, is associated with a poorer prognosis. Mortality in symptomatic AHF reaches up to 50% within one year of chemotherapy in patients who have not received prior cardiac treatment. Importantly, timely and appropriate management can lead to the resolution of AHF symptoms[6,11]. The incidence of chronic AIC is lower, reaching approximately 1.7%. It typically occurs within the first month of treatment, but may develop up to 10 years after the administration of a potentially cardiotoxic drug[6,12]. Consequently, anthracycline therapy during childhood and adolescence is a risk factor for cardiac dysfunction in adulthood[13,14]. A study conducted by the European Cancer Organization showed a reduction in left ventricular ejection fraction (LVEF) in up to 10% of patients treated with ACs, with 98% of cases occurring within the first year of treatment. Return to normal LVEF values was seen in only 11% of those who received pharmacological therapy for HF[8]. Similarly, an Australian study reported cardiotoxicity rates of 10.2%, with 15.4% of patients requiring hospitalisation for HF. The proportion of patients with complete, partial and no LVEF recovery over a median follow-up of 32 months were 16.3%, 29.3%, and 54.4%, respectively[15]. In another study, a 40-year incidence of HF and cardiovascular events (CVEs) in patients with Hodgkin lymphoma who had

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been treated with anthracyclines was 25% and 50%, respectively[16]. In a Polish study involving patients treated with ACs and cardioprotective angiotensin-converting enzyme inhibitors (ACE inhibitors), 18.5% of patients in the placebo group experienced a decreased LVEF, and nearly 30% showed an increase in N-terminal pro-B-type natriuretic peptide (NT-proBNP) (>125 pg/mL)[17].

The rates of cardiotoxicity depend on the type of anthracycline used, the size of individual doses, and the cumulative dose administered. There is a strong and well-documented relationship between cumulative AC dose and the risk of symptomatic HF[11]. When doxorubicin is administered at a cumulative dose of 500 mg/m^2, the risk of cardiotoxicity is approximately 16%; this risk increases significantly to about 36% when the dose exceeds 600 mg/m^2[3,6,10]. Although the maximum cumulative lifetime dose of ACs is generally considered to be 400–450 mg/m^2, cardiac complications have been reported even for doses ≤250 mg/m^2[11,18,19]. Other AIC risk factors include age (both <18 and >65 years), female gender in paediatric patients and male gender in adults, pre-existing cardiovascular conditions (such as HT or HF with reduced ejection fraction), genetic predisposition, concomitant use of other cardiotoxic anticancer agents (e.g. paclitaxel, trastuzumab, cyclophosphamide, etoposide, melphalan, and mitoxantrone), prior or concurrent chest radiotherapy (particularly involving the left side), as well as treatment protocols and the method of drug administration (intravenous bolus versus continuous infusion)[3,13,20].

Anthracycline-based chemotherapy has been shown to accelerate physiological aging, leading to a reduction in peak oxygen uptake (VO_{2peak}) equivalent to that observed in individuals 10–30 years older, as assessed by cardiopulmonary exercise testing, when compared to healthy controls[21].

Morphological and functional cardiac changes

Structural and functional myocardial changes in AIC resemble those observed in dilated cardiomyopathy. Most cancer patients present with normal LVEF both at diagnosis and following AC treatment, as assessed by conventional echocardiography[1–3]. However, more detailed strain assessment using speckle tracking echocardiograph (STE), which automatically tracks myocardial acoustic markers, can reveal subclinical left ventricular systolic dysfunction that may not be detected by conventional methods after cancer treatment[1,22–24]. These changes are often accompanied by left ventricular diastolic dysfunction. With progressing cardiotoxicity, structural remodelling, including enlargement and dilation of the cardiac chambers, can occur, ultimately leading to overt HF. In some patients, echocardiography may also detect mural thrombus. Global longitudinal strain (GLS) has been shown to be a more sensitive indicator of impaired myocardial contractility and early anthracycline-induced cardiomyopathy compared to the conventional LVEF assessment[22–24].

Histopathological changes

In anthracycline-induced cardiomyopathy, histopathological examination typically reveals heterogeneous interstitial myocardial fibrosis. Acute myocyte damage is uncommon, while extensive fibrotic regions interspersed with vacuolated cardiomyocytes, often referred to as "Adria cells", are more frequently observed. Myocytic vacuoles coalesce to form large, membrane-enclosed spaces, within which fibroblast proliferation and histiocyte infiltration are commonly observed. The loss of myofilaments is evidenced by the presence of residual Z-discs. Additional changes include dilation of the sarcoplasmic reticulum and T-tubules. The most characteristic histopathological features of anthracycline-induced cardiomyopathy include partial or complete loss of myofibrils, vacuolar degeneration of myocytes, nuclear and chromatin disintegration, and the replacement of chromatin with pale fibres[6,9].

Mechanisms of anthracycline-induced cardiomyopathy

The first anthracycline antibiotic, daunorubicin, was isolated in the 1960s from a strain of *Streptomyces peucetius*. This discovery was followed by the development of doxorubicin, an analogue distinguished by an additional hydroxyl group, derived from a mutant strain of *Streptomyces caesius*. Further research led to the synthesis of other clinically relevant analogues, including epirubicin and idarubicin[3,11]. The therapeutic mechanism of anthracyclines in cancer treatment involves inducing DNA damage and triggering apoptosis by inhibiting topoisomerase II activity. Anthracyclines disrupt DNA replication and transcription by forming complexes with topoisomerase II and intercalating into the DNA; this leads to the inhibition of macromolecule synthesis, generation of reactive oxygen species (ROS), and formation of DNA cross-links, ultimately resulting in apoptotic cell death[6,9,25]. It appears that the mechanisms underlying the antitumour effects of anthracyclines differ from those of cardiotoxicity, potentially making it difficult to find effective methods to prevent this complication. Data from preclinical and clinical studies are often contradictory. The pathophysiology of anthracycline-induced myocardial and cardiovascular changes is complex, multifactorial, and not fully understood. The primary mechanisms of AIC in myocardial cells include, among other things, increased oxidative stress, expressed by overproduction of reactive oxygen species (ROS) and lipid peroxidation, overproduction of reactive nitrogen species, forming cytotoxic complexes with DNA

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and the topoisomerase IIβ isoenzyme (TopIIβ), decreased levels of antioxidants and sulfhydryl groups, inhibition of nucleic acid and protein synthesis, release of vasoactive amines, disturbed calcium homeostasis, altered adrenergic function, influence on intracellular signalling via ErbB/HER family receptors in cardiomyocytes and decreased expression of heart-specific genes, although the list of potential mechanisms is much longer (Fig. 1). These pathological processes are often irreversible, and no cardioprotective treatment has been universally recommended for routine use at the onset of anticancer therapy[1,3,6,9,11,25].

Bioenergetic and functional mitochondrial impairment and cardiotoxicity

Mitochondria are a primary target of AC cardiotoxicity. Anthracyclines reduce intracellular ATP pools by impairing the structure and function of mitochondrial enzymes[11,26]. They disrupt the electron transport chain through multiple mechanisms, including the inhibition of mitochondrial complex I, cytochrome c activity, and the activity of sirtuin family members: sirtuin 1 (SIRT1) and sirtuin 3 (SIRT3), which may ultimately lead to apoptosis. ACs can inhibit SIRT1 and SIRT3, leading to the dysregulation of mitochondrial bioenergetics, increased ROS production in the electron transport chain, reduced activity of antioxidant enzymes, disruption of mitochondrial structure and function, and increased cytotoxicity. Additionally, SIRT1 activates genes involved in mitochondrial function, such as nuclear respiratory factor 1 (NRF-1), which may help protect cardiomyocytes from the effects of anthracyclines[11,27,28]. By modulating mitochondrial function, sirtuins have emerged as potential therapeutic targets for AIC[27,28]. Furthermore, anthracyclines irreversibly bind to cardiolipin, inhibiting its role as a cofactor for mitochondrial respiratory enzymes, and causing mitochondrial damage[29,30]. They can also interact with phospholipids, altering mitochondrial membrane properties and disrupting transporter activity and protein import, thereby contributing to cardiotoxicity[11,30,31].

Oxidative stress and ROS-induced cardiotoxicity

Oxidative stress is considered a key pathogenic factor in AIC, causing toxic mitochondrial damage in cardiomyocytes[11]. Numerous mitochondrial enzymes, including nicotinamide adenine dinucleotide (NADH) dehydrogenase, cytochrome P450 reductase, and xanthine oxidase, contribute to the generation of ROSs, such as superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2), which can be further converted into highly reactive hydroxyl radicals, or O_2^- may combine with nitric oxide to form peroxynitrite, a potent cytotoxic ROS. These intracellular oxidants activate p53, promoting cardiomyocyte apoptosis[11,32,33].

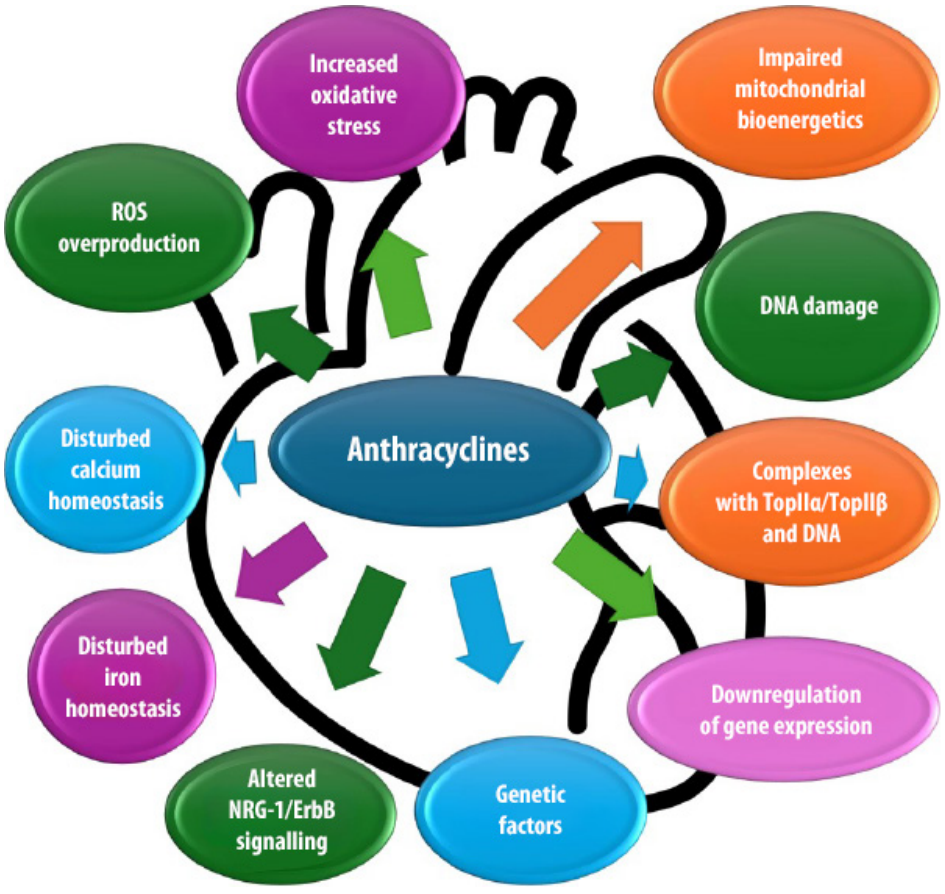

Fig. 1. Pathomechanisms underlying anthracycline-induced myocardial damage

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Redox reactions of the quinone moiety in anthracycline molecules enhance ROS production. Complexes formed with iron lead to lipid and protein peroxidation, impaired mitochondrial function, direct damage to the cell membrane, dysfunction of sodium-potassium adenosine triphosphatase, and direct damage to DNA structure[3]. These processes result in calcium ion accumulation, decreased ATP levels, and ultimately, cardiomyocyte apoptosis. ACs have also been shown to upregulate mRNA expression and enzymatic activity of xanthine oxidase, an enzyme located in the endoplasmic reticulum that promotes redox cycling. Cardiomyocytes are particularly susceptible to oxidative stress compared to other cell types due to their lower levels of antioxidant enzymes, such as catalase and glutathione peroxidase. Animal studies have confirmed the role of oxidative stress in the development of AIC[3,11,32,33].

Iron, ferroptosis and AIC

Iron overload may contribute to cardiotoxicity and cardiac damage following AC treatment, indicating a link between iron metabolism and AIC[11]. ACs can increase the labile iron pool by inactivating iron regulatory proteins 1 (IRP-1) and 2 (IRP-2) in cardiomyocytes. Doxycycline metabolites, by forming complexes with iron, can interfere with the regulatory function of IRP-1 and impair both iron uptake and storage[11,34,35]. Disrupted mitochondrial iron homeostasis has been shown to cause cardiomyocyte mitochondrial dysfunction by promoting ROS production, mitochondrial membrane depolarization, and mitochondrial oedema. Some ROSs, such as hydroxyl radicals arising from the dismutation of superoxide radicals (DOX–Fe^{2+} reaction with molecular oxygen), are resistant to enzymatic degradation and can modify key macromolecules essential for cardiomyocyte function[36,37]. A newly identified mechanism of cell damage/death, known as ferroptosis, has recently been implicated in anthracycline-induced cardiac injury. Ferroptosis is a form of regulated cell death characterized by iron-dependent lipid peroxidation. Studies have shown that cardiomyocytes exposed to anthracyclines exhibit features typical of ferroptosis-mediated cell death, and that inhibition of this process with ferrostatin-1 reverses anthracycline-induced cell death. ACs can induce ferroptosis via multiple mechanisms, many of which are not yet fully understood[11,38,39].

Calcium homeostasis and AIC

Disturbed calcium homeostasis can cause cardiac damage by inducing apoptosis and cardiomyocyte hypertrophy. Calcium leakage from the endoplasmic reticulum increases Ca^{2+} concentration in the mitochondrial matrix, leading to the opening of permeability transition pores in the inner mitochondrial membrane, which results in membrane depolarisation, matrix oedema, rupture of the outer membrane, and the release of pro-apoptotic signalling molecules, such as cytochrome c, from the intermembrane space[11,40,41]. An increased calcium level can activate calcineurin, a calcium-dependent phosphatase that plays a key role in mediating cardiac hypertrophy and apoptosis by dephosphorylating and activating the nuclear factor of activated T cells (NFAT). Studies have shown that anthracyclines induce nuclear translocation of NFAT, which is associated with increased expression of the target gene *FASLG*, encoding the FasL protein, ultimately leading to apoptosis[11,42]. Furthermore, anthracyclines disrupt Ca^{2+} homeostasis by modulating the expression and activity of multiple Ca^{2+}-binding proteins. Anthracyclines can upregulate the expression of TRPC3 (short transient receptor potential channel 3) and TRPC6 (short transient receptor potential channel 6) in cardiomyocytes and alter Ca^{2+} properties[11,43]. The anthracycline-induced increase in the expression of proteins related to oxidative stress and intracellular Ca^{2+} levels may be prevented by pharmacological inhibition of the TRPC channel[43]. Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) may be another factor contributing to AIC. By increasing CaMKII phosphorylation, anthracyclines may lead to CaMKII-mediated Ca^{2+} leakage into the endoplasmic reticulum and further associated adverse consequences[44].

Complex formation with topoisomerases IIα/IIβ and DNA and cardiotoxicity

Topoisomerase II (including TOPIIα and TOPIIβ) catalyses isomerization reactions that involve cleaving duplex DNA through the formation of a transient covalent protein–DNA cleavage complex[11,45]. Topoisomerase IIα (TOPIIα), a nuclear isoenzyme overexpressed in proliferating cancer cells, is the primary molecular target of anthracycline antitumor activity[3,11]. Non-dividing cells, such as cardiomyocytes, primarily express topoisomerase II. ACs interact with DNA and TOPIIα to form a ternary TOPII–doxorubicin–DNA complex that induces cell apoptosis. The ability to form ternary complexes with topoisomerases IIα/IIβ and DNA plays a key role in AIC[3,11,46,47]. By forming complexes with TOPIIβ, ACs gain the ability to intercalate with DNA, inducing the formation of double-helix breaks in DNA, leading to disruption of the replication process and apoptosis of cancer cells. These mechanisms result in mitochondrial dysfunction and apoptotic death of cardiomyocytes due to activation of the p53 protein[5,6]. Recent studies indicate that TOPIIβ may be the primary target of AIC[3]. Cardiomyocyte-specific deletion of TopIIβ has been shown to be protective against the development of AIC by reducing DNA double-strand breaks and apoptosis, as well as by normalising transcriptome changes associated with defective mitochondrial biogenesis[11,47]. Blocking and degradation of TopIIβ is currently considered the primary mechanism by which dexrazoxane mitigates AIC[11,48].

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DNA damage and AIC

AC treatment often causes irreversible changes in the expression of genes involved in mitochondrial function, glycolysis, and fatty acid oxidation in cardiomyocytes[11,49]. Furthermore, ACs damage both nuclear and mitochondrial DNA (mtDNA), the latter being more vulnerable due to its limited repair capacity and close proximity to the respiratory chain[11,12]. Mitochondrial DNA damage, mutations, and deletions have been observed in murine and human cardiomyocytes with anthracycline-induced cardiomyopathy[50,51]. ACs have been shown to reduce the activity of respiratory chain enzymes encoded by mtDNA, such as nicotinamide adenine dinucleotide dehydrogenase and cytochrome c oxidase, leading to impaired mitochondrial bioenergetics in cardiomyocytes[51]. This is due to the fact that mtDNA encodes up to 37 genes essential for the oxidative phosphorylation function of respiratory chain enzymes[52].

Gene expression and AIC

The anthracycline-induced reduction in the expression of contractile proteins such as α-actin, myosin light and heavy chains, troponin I, and desmin, is considered a potential mechanism contributing to cardiotoxicity. This leads to myofibril loss and impaired myocardial contractile function[6,53,54]. Additionally, decreased levels of sarcoplasmic reticulum ATPase may compromise myocardial diastolic function[53,54]. Doxorubicin can also inactivate extracellular signal-regulated kinase (ERK)[55].

Changes in neuregulin-1/ErbB signalling and cardiotoxicity

Signalling through the neuregulin-1 (NRG-1)/ErbB pathway is essential for maintaining normal cardiac muscle structure in adults. ErbB2 and ErbB4 receptors, members of the EGFR family, are receptor tyrosine kinases for which neuregulin-1 serves as a ligand[40]. AC treatment increases the sensitivity of cardiomyocytes to alterations in NRG-1/ErbB signalling. Animal studies suggest that short-term, intensive AC therapy reduces the number of cardiomyocyte ErbB4 receptors without affecting ErbB2 expression, while long-term therapy is associated with increased ErbB2 receptor expression[40,56].

The impact of genetic factors on cardiotoxicity

The considerable variability in the incidence of AIC suggests the involvement of genetic factors[57,58]. Genetic variants associated with AIC have been identified in approximately 20 genes, including *CELF4* (CUGBP Elav-like family member 4 involved in sarcomere structure and function), *RARG* (retinoic acid receptor gamma; regulates topoisomerase 2β expression), *SLC28A3* (solute carrier family 28 member 3; involved in drug transport), and *UGT1A6* (UDP glucuronosyltransferase family 1 member A6; involved in drug metabolism)[59]. However, other reports suggest even higher numbers by including additional genes, chromosomal regions, and, optionally, non-coding genomic sequences[60]. Identifying patients at high risk of cardiotoxic complications through genetic biomarkers could enable the early implementation of effective preventive and therapeutic strategies, as well as improved monitoring of these patients[61].

CONCLUSIONS

The pathomechanism of anthracycline-induced cardiotoxicity is complex and not yet fully understood. Exploring new biomarkers and advanced strategies to prevent anthracycline-induced myocardial dysfunction is essential to improve the quality of life and prognosis of cancer patients. Assessing an individual's risk of cardiotoxicity allows for the optimal selection of systemic treatment regimens, particularly when anthracyclines remain the cornerstone of therapy.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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Author contribution

Original concept of study; final approval of manuscript: AW, PK, BK, RD, GG, BUŻ, RM, WB. Collection, recording and/or compilation of data; analysis and interpretation of data; writing of manuscript: AW. Critical review of manuscript: PK, BK, RD, GG, BUŻ, RM, WB.

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