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CARDIOTOXICITY ASSOCIATED DURING NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER: A NARRATIVE REVIEW

Cardiotoxicidade Associada Durante a Quimioterapia Neoadjuvante no Câncer de Mama: Uma Revisão Narrativa

Cardiotoxicidad Asociada Durante la Quimioterapia Neoadyuvante en el Cáncer de Mama: Una Revisión Narrativa

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ABSTRACT

Neoadjuvant chemotherapy is a fundamental strategy in the treatment of breast cancer, enabling tumor reduction, increasing the feasibility of breast-conserving surgery, and treating micrometastatic disease. However, the use of specific chemotherapeutic agents has been associated with significant cardiovascular adverse effects, which may compromise treatment efficacy and patients' quality of life. To analyze current scientific evidence on cardiotoxicity associated with neoadjuvant chemotherapy in breast cancer, with emphasis on the main agents involved, risk factors, pathophysiological mechanisms, monitoring strategies, and clinical implications. This is a narrative literature review conducted through searches in PubMed, SciELO, and other relevant scientific journals. Studies published between 2013 and 2025 were included, encompassing reviews, meta-analyses, clinical trials, and clinical guidelines addressing cardiotoxicity related to neoadjuvant chemotherapy in breast cancer. The analyzed studies demonstrated that agents such as anthracyclines (doxorubicin, daunorubicin, epirubicin, and idarubicin), taxanes (paclitaxel and docetaxel), and anti-HER2 therapies (trastuzumab and pertuzumab) are strongly associated with cardiotoxicity. The main mechanisms include oxidative stress, topoisomerase IIβ dysfunction, reversible ventricular dysfunction, and cardiomyocyte injury. The incidence and severity of cardiotoxicity are influenced by risk factors such as advanced age, hypertension, diabetes mellitus, and pre-existing cardiovascular disease. Cardiotoxicity associated with neoadjuvant chemotherapy in breast cancer represents a significant clinical challenge, highlighting the importance of early recognition, appropriate cardiovascular monitoring, and individualized patient management. Preventive strategies and structured follow-up protocols are essential to minimize complications and optimize therapeutic outcomes.

Keywords: *Cardiotoxicity; Neoadjuvant Chemotherapy; Breast Cancer; Anthracyclines; Risk Factors.*

RESUMO

A quimioterapia neoadjuvante constitui uma estratégia fundamental no tratamento do câncer de mama, permitindo a redução tumoral, maior possibilidade de cirurgias conservadoras e o tratamento de micrometástases. Entretanto, o uso de determinados agentes quimioterápicos está associado a efeitos adversos cardiovasculares relevantes, que podem comprometer a continuidade do tratamento e a qualidade de vida das pacientes. O objetivo do estudo foi analisar as evidências científicas atuais sobre a cardiotoxicidade associada à quimioterapia neoadjuvante no câncer de mama, com ênfase nos principais agentes envolvidos, fatores de risco, mecanismos fisiopatológicos, estratégias de monitoramento e implicações clínicas. Trata-se de uma revisão narrativa da literatura, realizada por meio de buscas nas bases de dados PubMed, SciELO e outras revistas científicas relevantes. Foram incluídos estudos publicados entre 2013 e 2025, incluindo revisões, meta-análises, ensaios clínicos e diretrizes que abordassem a cardiotoxicidade relacionada à quimioterapia neoadjuvante no câncer de mama. Os estudos analisados demonstraram que agentes como antraciclinas (doxorrubicina, daunorrubicina, epirrubicina e idarubicina), taxanos (paclitaxel e docetaxel) e terapias anti-HER2 (trastuzumabe e pertuzumabe) estão fortemente associados ao desenvolvimento de cardiotoxicidade. Os principais mecanismos envolvidos incluem dano oxidativo, disfunção da topoisomerase IIβ,

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alterações reversíveis da função ventricular e lesão dos cardiomiócitos. A ocorrência e gravidade da cardiotoxicidade são influenciadas por fatores de risco como idade avançada, hipertensão arterial, diabetes mellitus e doenças cardiovasculares prévias. A cardiotoxicidade associada à quimioterapia neoadjuvante no câncer de mama representa um desafio clínico significativo, reforçando a importância do reconhecimento precoce, do monitoramento cardiovascular adequado e da abordagem individualizada das pacientes. Estratégias preventivas e protocolos de acompanhamento são essenciais para reduzir complicações e otimizar os desfechos terapêuticos.

Palavras-chave: Cardiotoxicidade; Quimioterapia Neoadjuvante; Câncer de Mama; Antraciclinas; Fatores de Risco.

RESUMEN

La quimioterapia neoadyuvante es una estrategia fundamental en el tratamiento del cáncer de mama, ya que permite la reducción tumoral, favorece cirugías conservadoras y contribuye al tratamiento de micrometástasis. No obstante, el uso de determinados agentes quimioterápicos se asocia a efectos adversos cardiovasculares relevantes, que pueden afectar la continuidad del tratamiento y la calidad de vida de las pacientes. Analizar la evidencia científica actual sobre la cardiotoxicidad asociada a la quimioterapia neoadyuvante en el cáncer de mama, con énfasis en los principales fármacos implicados, factores de riesgo, mecanismos fisiopatológicos, estrategias de monitoreo e implicaciones clínicas. Se realizó una revisión narrativa de la literatura mediante búsquedas en las bases de datos PubMed, SciELO y otras revistas científicas relevantes. Se incluyeron estudios publicados entre 2013 y 2025, tales como revisiones, metaanálisis, ensayos clínicos y guías clínicas que abordan la cardiotoxicidad relacionada con la quimioterapia neoadyuvante en el cáncer de mama. Los estudios analizados evidenciaron que agentes como las antraciclinas (doxorrubicina, daunorrubicina, epirrubicina e idarubicina), los taxanos (paclitaxel y docetaxel) y las terapias anti-HER2 (trastuzumab y pertuzumab) se asocian de forma significativa con el desarrollo de cardiotoxicidad. Los principales mecanismos incluyen estrés oxidativo, disfunción de la topoisomerasa IIβ, alteraciones reversibles de la función ventricular y daño de los cardiomiocitos. La aparición y gravedad de la cardiotoxicidad están influenciadas por factores de riesgo como edad avanzada, hipertensión arterial, diabetes mellitus y enfermedades cardiovasculares previas. La cardiotoxicidad asociada a la quimioterapia neoadyuvante en el cáncer de mama constituye un desafío clínico relevante, lo que refuerza la necesidad de un reconocimiento precoz, un monitoreo cardiovascular adecuado y un manejo individualizado de las pacientes. La implementación de estrategias preventivas y protocolos de seguimiento es esencial para reducir complicaciones y optimizar los resultados terapéuticos.

Palabras clave: *Cardiotoxicidad; Quimioterapia Neoadyuvante; Cáncer de Mama; Antraciclinas; Factores de Riesgo.*

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1. INTRODUCTION

Neoadjuvant chemotherapy refers to systemic antineoplastic treatment administered prior to surgery or, in some cases, before radiotherapy, with the primary aim of reducing tumor size, thereby enabling and facilitating surgical resection. It is also employed to preserve organs and anatomical structures, such as the breast, allowing for less mutilating surgical procedures. In addition, neoadjuvant chemotherapy plays a crucial role in the early treatment of micrometastases that are not yet detectable by imaging or laboratory examinations. Tumor response to neoadjuvant chemotherapy provides valuable guidance for surgical decision-making and contributes to improved oncological outcomes.

In this context, there has been growing concern regarding the incidence of breast cancer in the southeastern region of Brazil between 2023 and 2024. In 2023, the Southeast presented an age-adjusted incidence rate of 81.06 cases per 100,000 women, the highest among all Brazilian regions. Breast cancer in this population encompasses different molecular subtypes, including Luminal A (HER2-negative with low proliferative index), Luminal B (HER2-positive or negative with higher proliferative index), HER2-positive (HER2 overexpression), and triple-negative breast cancer (negative for estrogen receptor [ER], progesterone receptor [PR], and HER2, and typically associated with high histological grade).

Furthermore, a national study conducted between 2023 and 2024 evaluated 176 patients diagnosed with triple-negative breast cancer treated within the Brazilian Unified Health System (Sistema Único de Saúde – SUS). The study revealed that 10.8% of patients received neoadjuvant chemotherapy, while 89.2% underwent adjuvant chemotherapy. The most frequently used therapeutic regimen was the combination of doxorubicin, cyclophosphamide, and a taxane, accounting for 80.7% of cases. In this regard, neoadjuvant chemotherapy represents a key therapeutic strategy in breast cancer management, particularly in patients with locally advanced or inflammatory HER2-positive disease.

Within this framework, the present study aims to highlight the relevance of cardiotoxicity associated with neoadjuvant chemotherapy in breast cancer treatment. This concern is primarily related to the chemotherapeutic agents commonly employed, such as anthracyclines—especially doxorubicin and epirubicin—which are well known for their cardiotoxic potential. Additionally, trastuzumab has been associated with left ventricular dysfunction and heart failure, particularly when administered in combination with anthracyclines.

Moreover, cardiotoxic effects are not always immediate during treatment, underscoring the need for careful and long-term surveillance. Cardiac monitoring through echocardiography, assessment of left ventricular ejection fraction, and evaluation of cardiac biomarkers is essential, as cardiotoxicity may manifest years after the completion of therapy. Importantly, cardiotoxicity may also negatively impact prognosis, as it can lead to interruption or reduced efficacy of oncological treatment by compromising tumor response. Consequently, it may result in chronic cardiovascular morbidity, adversely affecting quality of life and overall survival, even in cases where cancer control is achieved.

2. METHODOLOGY

This study consists of a narrative literature review conducted to explore cardiotoxicity associated with neoadjuvant chemotherapy in patients with breast cancer. Articles published between 2013 and 2025 were selected, including review articles, meta-analyses, clinical trials, and national and international guidelines. The literature search was performed across multiple databases, including PubMed, SciELO, MDPI, JAMA, Frontiers, and other leading journals in the fields of oncology and cardio-oncology.

The search strategy incorporated the following keywords: “cardiotoxicity,” “neoadjuvant chemotherapy,” “breast cancer,” “anthracyclines,” “trastuzumab,” “taxanes,” and “risk factors,” in Portuguese, English, and Spanish. The selected studies were critically evaluated based on clinical relevance, type of chemotherapeutic agent, described mechanisms of cardiotoxicity, cardiac monitoring strategies, and associated risk factors.

Duplicate studies or those containing insufficient or incomplete data were excluded, ensuring the selection of consistent and reliable evidence for narrative analysis and critical synthesis of the findings.

3. DEVELOPMENT

Neoadjuvant chemotherapy represents a fundamental strategy for the success of several oncological treatments; however, the chemotherapeutic agents employed may induce multiple cardiovascular adverse effects, potentially leading to acute or late-onset heart failure. Such complications may require modification, temporary suspension, or permanent discontinuation of antineoplastic therapy, thereby exerting a substantial negative impact on patients’ quality of life and

overall survival.

Accordingly, the development of cardiotoxicity varies according to drug class, cumulative dose, route of administration, and treatment duration, in addition to individual risk factors such as hypertension, obesity, smoking, physical inactivity, and metabolic disorders. Importantly, cardiotoxic effects may be reversible or irreversible depending on the therapeutic strategy and clinical management. Therefore, there is a significant need for cardioprotective approaches aimed at reducing the incidence and severity of cardiotoxicity during neoadjuvant chemotherapy.

Anthracyclines are currently considered a cornerstone in breast cancer treatment. The most commonly used agents include doxorubicin (Adriamycin), daunorubicin (daunomycin), epirubicin, and idarubicin. Their antineoplastic mechanism of action involves DNA intercalation, whereby these agents insert between DNA base pairs, preventing helix unwinding and thereby inhibiting transcription and replication in rapidly proliferating tumor cells. Additionally, anthracyclines inhibit topoisomerase IIα, an enzyme highly expressed in breast cancer cells. By blocking the religation of DNA strand breaks induced by this enzyme, anthracyclines promote the accumulation of DNA damage, ultimately triggering apoptotic cell death. Furthermore, anthracyclines generate reactive oxygen species (ROS) through iron-mediated redox reactions, leading to lipid peroxidation, protein damage, and additional DNA strand breaks. Recent evidence also suggests that anthracyclines modulate the tumor microenvironment by inducing immunogenic cell death, releasing signals that activate antitumor immune responses.

Common anthracycline-based regimens include AC (doxorubicin plus cyclophosphamide, frequently followed by a taxane), FEC (fluorouracil, epirubicin, and cyclophosphamide), and EC-T (epirubicin plus cyclophosphamide followed by docetaxel). Close monitoring of these combinations is essential, as anthracyclines are vesicant agents, and extravasation may result in severe skin and tissue necrosis. Moreover, due to their large volume of distribution and pharmacokinetic properties, these drugs do not efficiently cross the blood–brain barrier—partly mediated by P-glycoprotein activity—leading to relative accumulation in the liver, bone marrow, and myocardium. Hepatic metabolism via aldo-keto and carbonyl reductases generates active alcohol metabolites, such as doxorubicinol, which are strongly associated with cardiotoxicity. Although anthracyclines exhibit terminal half-lives of approximately 20–40 hours, some metabolites persist longer, contributing to cumulative tissue toxicity.

The mechanisms underlying anthracycline-induced cardiotoxicity are multifactorial. A

predominance of the topoisomerase IIβ isoform in cardiomyocytes has been identified, and its inhibition leads to DNA damage, downregulation of PGC-1α/β, impaired mitochondrial biogenesis, and subsequent energetic failure of cardiac myocytes. In addition, ROS generation in the presence of iron is particularly deleterious in myocardial tissue, which is characterized by high metabolic demand and limited antioxidant capacity. Alcoholic metabolites further disrupt calcium (Ca^{2+}) handling and membrane function in cardiomyocytes. Clinically, these mechanisms result in cumulative, dose-dependent cardiotoxicity, with risk increasing proportionally to the total cumulative dose expressed in mg/m^2, and notably, no dose can be considered completely risk-free.

Anthracyclines enter cardiac cells not through passive diffusion, but via specific transporters, including SLC28 and SLC29 nucleoside transporters and organic anion transporting polypeptides (OATPs). These transporters regulate intracellular drug concentrations and, consequently, toxicity. Anthracycline-induced cardiac injury can be broadly classified into acute and chronic forms. Acute cardiac toxicity typically manifests within days of drug administration and is characterized by acute myocarditis, cardiomyocyte injury, inflammatory infiltrates, and interstitial edema. Chronic cardiotoxicity, in contrast, develops after multiple chemotherapy cycles and is associated with progressive and often asymptomatic decline in cardiac function, eventually leading to congestive heart failure.

Trastuzumab is a humanized IgG1 monoclonal antibody primarily used in the treatment of HER2-positive breast cancer, as well as selected cases of HER2-positive gastric cancer. The HER2 gene encodes a transmembrane receptor that is overexpressed in tumor cells, promoting uncontrolled cellular proliferation. Trastuzumab binds specifically to domain IV of the HER2 receptor, thereby blocking proliferative signaling through the PI3K/Akt and MAPK pathways. It also prevents receptor cleavage, reducing the formation of truncated, constitutively active HER2 variants. Additionally, trastuzumab induces antibody-dependent cellular cytotoxicity (ADCC), marking tumor cells for immune-mediated destruction.

Despite its clinical efficacy, trastuzumab is frequently combined with pertuzumab, particularly in neoadjuvant settings. Importantly, cardiotoxicity associated with anti-HER2 therapies is generally considered reversible. Pertuzumab binds to domain II of the HER2 receptor, a critical region for dimerization with other HER family receptors, particularly HER3—the most oncogenically potent dimer. By preventing HER2/HER3 dimerization, pertuzumab disrupts downstream PI3K/Akt and

MAPK signaling pathways. Because trastuzumab and pertuzumab bind to distinct HER2 epitopes, they act synergistically without competition, resulting in more comprehensive blockade of HER2 signaling: trastuzumab inhibits ligand-independent signaling, while pertuzumab prevents receptor dimerization.

It is also essential to address the cardiotoxic effects of taxanes and platinum-based agents, as they are widely used in neoadjuvant chemotherapy and administered to approximately 50% of patients with breast cancer. Taxanes such as paclitaxel and docetaxel exert their antitumor effects by inhibiting microtubule depolymerization, thereby disrupting mitosis and preventing tumor cell proliferation. However, taxanes have been associated with cardiotoxic effects, including QT interval prolongation and ventricular arrhythmias such as torsades de pointes. These effects are attributed to paclitaxel-induced interference with cardiac ion channels, particularly potassium channels, resulting in impaired ventricular repolarization.

Another relevant manifestation of taxane-related cardiotoxicity is ventricular dysfunction independent of anthracycline exposure. Evidence suggests direct cardiomyocyte toxicity mediated by oxidative stress, mitochondrial alterations, and intracellular accumulation of microtubules, which disrupts intracellular transport within cardiac cells.

Interactions between taxanes and anthracyclines further increase cardiotoxic risk. Taxanes reduce hepatic metabolism of doxorubicin, leading to increased plasma concentrations and enhanced antitumor efficacy, but also significantly elevating the risk of heart failure when used concomitantly. Moreover, paclitaxel infusion may induce histamine release, resulting in bradycardia, atrioventricular conduction blocks, and other arrhythmias.

Platinum-based agents, including cisplatin, carboplatin, and oxaliplatin, exert their antineoplastic effects through DNA crosslink formation, thereby inhibiting replication and transcription and inducing tumor cell death. Nevertheless, their cardiotoxic potential is clinically relevant. Cisplatin induces ROS production, leading to endothelial injury, platelet activation, and chronic vascular dysfunction, which may increase the risk of myocardial infarction, stroke, and premature atherosclerosis. Additionally, cisplatin may cause hypomagnesemia and hypocalcemia, altering cardiomyocyte membrane potentials and predisposing patients to arrhythmias. Cases of coronary vasospasm and acute arterial thrombosis have also been reported.

Recent studies and Brazilian cardio-oncology guidelines have evaluated patients with breast cancer treated with anthracyclines in both neoadjuvant and adjuvant settings, with the primary

objective of identifying clinical risk factors associated with increased cardiotoxicity. The main risk factors identified include obesity, hypertension, advanced age, pre-existing cardiovascular disease (such as heart failure or coronary artery disease), and diabetes mellitus.

Hypertension represents a major risk factor due to reduced myocardial reserve resulting from chronic pressure overload, which induces hypertrophy, fibrosis, and subclinical dysfunction, including impaired global longitudinal strain (GLS). Consequently, the left ventricle becomes less compliant and more vulnerable to the toxic stress induced by anthracyclines and HER2 blockade. Hypertension-associated endothelial and microvascular dysfunction further exacerbates mitochondrial oxidative stress caused by anthracyclines, contributing to declines in left ventricular ejection fraction (LVEF). Elevated blood pressure also increases wall stress, and when combined with agents that reduce contractile reserve, the likelihood of LVEF reduction and heart failure increases. Moreover, hypertrophied myocardium relies more heavily on HER2/neuregulin-1 signaling; thus, blockade of this pathway with trastuzumab ± pertuzumab in hypertensive hearts facilitates cancer therapy–related cardiac dysfunction (CTRCD), defined as an LVEF reduction ≥10% or below 50%.

Advanced age is another significant risk factor in neoadjuvant chemotherapy, owing to age-related reductions in myocardial reserve caused by increased fibrosis, diastolic dysfunction, and heightened susceptibility to oxidative stress and impaired repair mechanisms. The higher prevalence of comorbidities and polypharmacy in elderly patients further amplifies myocardial and microvascular injury during the intensive neoadjuvant treatment phase. Consequently, cumulative anthracycline exposure combined with advanced age produces a dynamically increasing risk of ventricular dysfunction, particularly when anti-HER2 therapies are used concomitantly.

Diabetes mellitus and prediabetes are also recognized risk factors for cardiotoxicity in breast cancer patients receiving neoadjuvant chemotherapy. Diabetes reduces nitric oxide bioavailability, increases endothelial permeability, and promotes microvascular dysfunction, thereby impairing coronary microcirculation and myocardial metabolic exchange. Furthermore, diabetes is associated with increased ROS production and pro-inflammatory cytokine release, which synergize with anthracycline-induced mitochondrial damage, amplifying cardiomyocyte injury and apoptosis. Diabetes also promotes myocardial hypertrophy, interstitial fibrosis, and subclinical diastolic dysfunction, rendering reductions in contractility more likely to progress to clinically overt heart failure.

The primary goal of neoadjuvant therapy is tumor downstaging, enabling breast-conserving surgery and reducing the need for extensive axillary lymph node dissection, thereby decreasing morbidity. Early tumor assessment is essential for prognostic stratification and includes serial physical examinations to evaluate palpable changes in breast volume prior to each cycle, imaging studies such as ultrasonography to assess tumor and lymph node reduction, mammography to evaluate residual microcalcifications, and magnetic resonance imaging, which is the most sensitive modality for quantifying tumor reduction, particularly in multifocal or dense tumors.

In addition to imaging, biomarkers such as Ki-67, a cellular proliferation index, are useful indicators of treatment response, with reductions during therapy suggesting therapeutic efficacy. Although these assessment methods offer significant clinical benefit, insufficient response warrants treatment regimen modification during therapy to improve final outcomes. Achieving pathological complete response (pCR) is associated with improved overall and disease-free survival, particularly in HER2-positive and triple-negative breast cancer. Early identification of resistant tumors is essential to avoid unnecessary toxicity and delays; in severe cases, early surgical planning may be required, as rapid responders may benefit from earlier breast-conserving surgery.

Personalized treatment planning is essential, particularly for partially responsive tumors, which may be managed with segmental surgery combined with radiotherapy. Non-responsive tumors may require more extensive surgical approaches or additional adjuvant regimens. Brazilian and international studies demonstrate that patients receiving neoadjuvant chemotherapy exhibit higher rates of breast-conserving surgery, especially in HER2-positive and triple-negative tumors. Continuous assessment enables intra-treatment decision-making, reducing the risk of unnecessarily extensive surgical procedures.

The selection of neoadjuvant therapy is ultimately guided by pCR or partial response outcomes. Patients who do not achieve pCR may receive additional adjuvant chemotherapy, such as capecitabine in triple-negative tumors or targeted therapy in HER2-positive disease. Molecular subtype must also be considered: HER2-positive tumors warrant continuation or initiation of anti-HER2 therapy (trastuzumab ± pertuzumab), hormone receptor–positive tumors require adjuvant endocrine therapy, and triple-negative tumors may benefit from adjuvant immunotherapy when clinically indicated.

4. RESULTS

The analyzed studies indicate that cardiotoxicity associated with neoadjuvant chemotherapy occurs through multiple cellular and molecular mechanisms. In cardiac cells, there is a predominance of the Topoisomerase IIβ (Topo IIβ) isoform, whose inhibition by anthracyclines leads to DNA strand breaks, downregulation of PGC-1α/β, and impaired mitochondrial biogenesis, resulting in cardiomyocyte energetic failure. In addition, the generation of reactive oxygen species (ROS) and free iron, combined with the high metabolic demand and limited antioxidant capacity of the myocardium, promotes oxidative stress and cellular injury. Alcoholic metabolites of anthracyclines disrupt Ca^{2+} handling and cell membrane function, contributing to cumulative and dose-dependent myocardial dysfunction.

Anthracyclines (doxorubicin, daunorubicin, epirubicin, and idarubicin) enter cardiomyocytes through specific transporters, including SLC28, SLC29, and organic anion transporting polypeptides (OATPs), thereby determining intracellular drug concentration and toxicity. Clinically, cardiotoxic effects manifest as acute cardiac injury—occurring within days and characterized by myocarditis, inflammatory infiltrates, and interstitial edema—or as chronic, subclinical injury marked by progressive ventricular dysfunction and increased risk of heart failure. Anthracycline-associated cardiotoxicity is cumulative and proportional to the total administered dose, with no dose being completely risk-free.

Anti-HER2 monoclonal antibodies, such as trastuzumab and pertuzumab, act through distinct mechanisms by blocking PI3K/Akt and MAPK signaling pathways and inducing antibody-dependent cellular cytotoxicity. Although highly effective against HER2-positive tumor cells, both agents may induce cardiotoxicity, which is generally reversible. Trastuzumab binds to domain IV of the HER2 receptor, whereas pertuzumab targets domain II, preventing HER2/HER3 dimerization and promoting therapeutic synergy. Cardiac monitoring is strongly recommended, particularly when these agents are administered in combination with anthracyclines.

Taxanes, including paclitaxel and docetaxel, inhibit microtubule depolymerization, thereby blocking mitosis. However, they may also induce cardiotoxicity, including sinus bradycardia, QT interval prolongation, ventricular arrhythmias, and ventricular dysfunction, which are often reversible. Concomitant use with anthracyclines increases cardiac risk, as taxanes elevate plasma concentrations of doxorubicin, potentiating adverse effects. Platinum-based agents, such as cisplatin, carboplatin, and

oxaliplatin, also contribute to cardiotoxicity by inducing oxidative stress, endothelial dysfunction, and electrolyte disturbances, thereby increasing the risk of myocardial infarction, stroke, and arrhythmias.

Overall, cardiotoxicity associated with neoadjuvant chemotherapy in breast cancer is multifactorial and depends on the type of drug, cumulative dose, individual risk factors (advanced age, hypertension, diabetes, and pre-existing cardiovascular disease), and therapeutic combinations. Monitoring strategies, including assessment of ventricular function, cardiac biomarkers, and continuous clinical follow-up, are essential to reduce complications and ensure therapeutic success without compromising oncological efficacy.

5. DISCUSSION

The reviewed literature consistently demonstrates that cardiotoxicity represents a clinically significant complication and a persistent concern during neoadjuvant chemotherapy in patients with breast cancer. This toxicity is primarily mediated by oxidative damage and dysfunction of topoisomerase IIβ in cardiomyocytes. Notably, the same molecular mechanisms responsible for myocardial injury are also fundamental to the antitumor efficacy of these agents, highlighting the complexity of balancing oncological benefit against cardiovascular risk.

Cardiac injury may present as either acute or chronic toxicity. Acute manifestations include myocarditis, interstitial edema, and cellular injury occurring within days of chemotherapy administration. In contrast, chronic toxicity develops insidiously and progressively, leading to ventricular dysfunction and, in some cases, overt heart failure. Importantly, many of these alterations may be reversible; however, inadequate monitoring increases the risk of irreversible damage, directly impairing patients' quality of life.

Among chemotherapeutic agents, anthracyclines (doxorubicin, daunorubicin, epirubicin, and idarubicin) are most strongly associated with cardiotoxicity. Their uptake into cardiomyocytes via transporters such as SLC28, SLC29, and OATPs determines intracellular drug accumulation and the extent of myocardial damage. The underlying mechanisms include ROS generation, altered calcium homeostasis, and mitochondrial dysfunction, culminating in energetic failure and cardiomyocyte apoptosis.

Anti-HER2 monoclonal antibodies, including trastuzumab and pertuzumab, also pose cardiovascular risk, albeit typically reversible. Trastuzumab blocks domain IV of the HER2 receptor,

inhibiting proliferative signaling and promoting antibody-dependent cytotoxicity, while pertuzumab binds to domain II, preventing receptor dimerization with HER3 and enhancing therapeutic synergy. Despite their clinical efficacy in HER2-positive tumors, careful monitoring of cardiac function is mandatory during treatment.

Taxanes, such as paclitaxel and docetaxel, contribute to cardiotoxicity by interfering with cardiac ion channels, prolonging the QT interval, and predisposing patients to ventricular arrhythmias. They may also induce ventricular dysfunction independently of anthracyclines through oxidative stress, mitochondrial alterations, and intracellular microtubule accumulation, impairing intracellular transport. When combined with anthracyclines, taxanes further increase cardiac risk by elevating plasma anthracycline concentrations and, consequently, the likelihood of heart failure.

Platinum-based agents, including cisplatin, carboplatin, and oxaliplatin, although effective through DNA crosslink formation and inhibition of tumor cell replication, also exhibit clinically relevant cardiotoxicity. These agents promote oxidative stress, endothelial injury, vascular dysfunction, and electrolyte imbalances, increasing the risk of myocardial infarction, stroke, and arrhythmias. Reports of coronary vasospasm and acute arterial thrombosis further underscore the need for vigilant clinical assessment.

Individual risk factors—such as advanced age, hypertension, diabetes mellitus, and pre-existing cardiovascular disease—significantly increase susceptibility to cardiotoxicity. Patients presenting multiple risk factors require individualized assessment before, during, and after chemotherapy. The reviewed studies also reveal variability in cardiotoxicity definitions and follow-up duration across oncological guidelines and specialized journals, complicating direct comparison of outcomes while reinforcing the clinical relevance of the observed evidence.

Finally, the findings indicate that future research should prioritize preventive interventions and standardized monitoring protocols. Strategies such as periodic assessment of ventricular function, cardiac biomarkers, and continuous clinical follow-up are essential to reduce complications and ensure that patients derive maximal benefit from chemotherapy without compromising cardiovascular health.

6. CONCLUSION

In contemporary medical practice, certain therapeutic interventions, while effective in achieving specific oncological objectives, may trigger relevant systemic adverse effects. Neoadjuvant chemotherapy exemplifies this paradox, as it promotes substantial tumor control and improves surgical resectability, yet carries a significant risk of cardiotoxicity that compromises the structural and functional integrity of the cardiovascular system. Moreover, its effects extend beyond the myocardium, adversely influencing multiple physiological systems and exerting a complex impact on the patient's overall clinical status.

This review demonstrates that cardiotoxicity represents a major challenge in the neoadjuvant treatment of breast cancer, particularly due to the use of anthracyclines, taxanes, and anti-HER2 agents. Although these drugs are essential for tumor control and for increasing pathological complete response rates, their cardiovascular adverse effects may compromise therapeutic efficacy and patients' quality of life. Advanced age, hypertension, diabetes, and pre-existing cardiovascular disease further increase vulnerability to cardiac toxicity, emphasizing the importance of individualized risk assessment.

In this context, serial monitoring through echocardiography, cardiac biomarkers, and multidisciplinary clinical follow-up is indispensable for early detection and implementation of cardioprotective strategies, thereby reducing the risk of irreversible complications. Consequently, the development of standardized protocols for cardiotoxicity prevention and management, as well as further research into less cardiotoxic therapeutic approaches, is imperative. Such measures will enable the reconciliation of oncological efficacy with cardiovascular preservation, ensuring greater safety and improved quality of life for patients undergoing treatment.

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