Pathophysiology of cardiotoxicity induced by nonanthracycline chemotherapy

Clelia Madeddu, Martino Deidda, Alessandra Piras, Christian Cadenu, Laura Demurtas, Marco Puzzoni, Giovanna Piscopo, Mario Scartozzi and Giuseppe Mercuro

The risk and mechanism of chemotherapy-induced cardiotoxicity (CTX) vary depending on the type and intensity of the anticancer regimen. Myriad chemotherapeutic drugs produce adverse cardiovascular effects such as arterial hypertension, heart failure, and thromboembolic events. Among the numerous classes of these drugs, anthracyclines have been studied most extensively because of their overt cardiovascular effects and the high associated incidence of heart failure. However, CTX might also be caused by other types of chemotherapeutic agents, including alkylating agents (cyclophosphamide, ifosfamide), platinum agents, antimetabolites (5-fluorouracil, capecitabine), antibiotics (mitoxantrone, mitomycin, bleomycin), and antimitotubule agents (taxanes). Here, we review the incidence, clinical impact, and potential mechanisms of CTX associated with nonanthracycline chemotherapy used for cancer patients. The published data support a marked increase in CTX risk, particularly with certain drugs such as 5-fluorouracil and cisplatin. Each anticancer regimen is associated with distinct modes of heart damage, both symptomatic and asymptomatic. However, the underlying mechanisms of CTX have been established only in a few cases, and only few nonanthracycline chemotherapeutics (mitoxantrone, mitomycin, ifosfamide) act through a recognizable mechanism and show a predictable dose dependence. Lastly, nonanthracycline chemotherapy can induce both chronic lesions, such as systolic dysfunction, and acute lesions, such as the ischemia that occurs within hours or days after treatment. An increased understanding of the mechanisms, and potential therapeutic targets of CTX induced by various nonanthracycline chemotherapeutic agents is clearly required.

Keywords: cardiotoxicity, 5-fluorouracil, oxidative stress, platinum, taxanes

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Introduction
Chemotherapy-induced cardiotoxicity (CTX) was defined by the Cardiac Review and Evaluation Committee of Trastuzumab-associated CTX as one or more of the following: a reduction in left ventricular ejection fraction (LVEF) from baseline by at least 5% to less than 55% in the presence of symptoms or heart failure or an asymptomatic reduction in LVEF by at least 10% to less than 55%; cardiomyopathy in terms of a reduction in LVEF by at least 5% to less than 55%; electrocardiographic changes such as systolic dysfunction, and acute lesions, such as the ischemia that occurs within hours or days after treatment. Anticancer therapy exerts a combination of ‘on target’ effects, which counteract the undesirable proliferation of cancer cells, and ‘off target’ effects, which negate the protective effects of cardiomyocytes and endothelial cells, especially in response to stress.

CTX incidence and pathophysiology differ depending on the type, cumulative dose, and administration schedule of antiblastic therapy. The use of numerous chemotherapy drugs is associated with adverse cardiovascular effects such as congestive heart failure, myocardial ischemia, hypertension, thromboembolic complications, arrhythmias, and conduction disturbances. Among these drugs, anthracyclines have been studied most extensively because of their ability to induce cardiac injury, particularly heart failure. However, CTX might also be caused by other classes of chemotherapeutic agents (Table 1), such as alkylating agents (cyclophosphamide, ifosfamide), platinum agents, antimetabolites (5-fluorouracil, capecitabine), antibiotics (mitomycin, bleomycin), and antimitotubule agents (taxanes).

The cardiotoxic effects produced by antineoplastic agents can be permanent (type I CTX) or reversible (type II), and can be induced at distinct levels and intensities. A distinguishing feature of type I chemotherapy-induced CTX is the induction of cardiomyocyte...
In terms of onset, CTX can develop in an acute, subacute, or chronic manner. Acute or subacute CTX is characterized by abnormalities of ventricular repolarization and electrocardiographic QT-interval changes, supraventricular and ventricular arrhythmias, or acute coronary syndromes and pericarditis and/or myocarditis-like syndromes, observed at any time from the initiation of therapy to as much as 2 weeks after treatment termination. Conversely, chronic CTX can be differentiated – based on the onset of clinical symptoms – into two subtypes: early, within 1 year after termination of chemotherapy; or late, more than 1 year after chemotherapy. The most typical sign of chronic CTX is asymptomatic systolic and/or diastolic LV dysfunction, which could lead to dilated cardiomyopathy. Nonanthracycline chemotherapy might induce chronic toxicity in the form of LV systolic dysfunction and also induce acute injuries such as ischemia, which occur within hours or days after the start of treatment. Moreover, current evidence indicates that the use of nonanthracycline chemotherapeutics is also associated with a CTX risk throughout the life of the patient.

**Pathophysiology**

The mechanisms of CTX associated with nonanthracycline chemotherapeutics differ widely among several agents. One of these mechanisms is represented by the ability of the drugs to either directly damage cardiomyocytes or cause pericardium inflammation. For example, paclitaxel-induced CTX is mediated by direct damage of cardiac muscle cells through the drug’s actions on subcellular organelles. In the case of 5-fluorouracil, the toxic effect exerted by the drug on the vascular endothelium involves the dysregulation of endothelial nitric oxide synthase and the induction of protein kinase C, and this leads to coronary spasm and endothelial-to-endothelial cell adhesion.

Certain drugs might affect the coagulation system and predispose to thromboembolic events. The coagulation cascade is altered mainly through damage of the vascular intima, which predisposes to thrombosis. Cisplatin, in particular, can enhance platelet aggregation and thromboxane formation, and activate arachidonic acid pathways.

Anticancer agents might exacerbate atrial fibrillation, which could be a preexisting condition, especially in elderly cancer patients. Atrial fibrillation could be induced by ifosfamide, gemcitabine, melphalan, cisplatin, docetaxel, 5-fluorouracil, or etoposide.

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**Table 1 Main features and mechanisms of cardiotoxicity from nonanthracycline chemotherapy**

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<thead>
<tr>
<th>Drugs</th>
<th>Cardiotoxicity</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents (cyclophosphamide, ifosfamide)</td>
<td>Acute myopericarditis</td>
<td>Direct endothelial injury¹⁸⁰¹⁰⁰</td>
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<tr>
<td></td>
<td>Cardiac tamponade</td>
<td>Oxidative stress and mitochondrial damage¹⁰⁰</td>
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<tr>
<td></td>
<td>Arrhythmias</td>
<td>Glutathione S-transferase P (GSTP) deficiency¹⁰⁰</td>
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<td></td>
<td>Heart failure (high dose)</td>
<td>Reduced expression of heart fatty acid-binding protein and carnitine palmityltransferase¹⁰⁰</td>
</tr>
<tr>
<td>Platinum</td>
<td>Electrocardiographic changes</td>
<td>Direct myocytes injury¹⁰⁰</td>
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<td>Angina</td>
<td>Oxidative stress¹⁰⁰</td>
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<td>Arrhythmias</td>
<td>Mitochondrial ultrastructural abnormalities¹⁰⁰</td>
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<td>Myocarditis</td>
<td>Platelet activation and aggregation¹⁰⁰</td>
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<td>Cardiomyopathy</td>
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<td>Congestive heart failure</td>
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<td></td>
<td>Acute myocardial infarction</td>
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<td></td>
<td>Increased thrombotic events</td>
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<td>Ref.¹⁰⁰–¹⁰⁰¹⁰⁰</td>
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<tr>
<td>Antimetabolites (fluorouracil and capecitabine)</td>
<td>Angina-like chest pain</td>
<td>Coronary artery thrombosis</td>
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<td></td>
<td>Myocardial infarction</td>
<td>Arteritis</td>
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<tr>
<td></td>
<td>Arrhythmias</td>
<td>Vasospasm²²</td>
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<td></td>
<td>Ventricular tachycardia</td>
<td>Oxidative stress in myocardiocytes and endothelial cells²³</td>
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<td></td>
<td>Heart failure and cardiogenic shock</td>
<td>Citrate accumulation and Krebs cycle alteration²⁴</td>
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<td>QT prolongation with torsades de pointes</td>
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<tr>
<td></td>
<td>Ref.²⁴,²⁷</td>
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<tr>
<td>Antibiotics (mitoxantrone, bleomycin mitomycin C)</td>
<td>Arrhythmias</td>
<td>Oxidative stress²⁸</td>
</tr>
<tr>
<td></td>
<td>Diastolic dysfunction</td>
<td>Damage of mitochondrial respiratory chain and impaired energy metabolism²⁹</td>
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<td>Ischemic heart disease</td>
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<td>Chronic heart failure</td>
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<td>Myocardial ischemia</td>
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<td>Damage on Purkinje system or autonomic control³³</td>
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<tr>
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<td></td>
<td>Induction of histamine release³⁴</td>
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<td>Enhanced metabolism of doxorubicin toxic species³⁵</td>
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<td>Antimicrotubule agents (paclitaxel and docetaxel)</td>
<td>Bradycardia</td>
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<td>Atroventricular block</td>
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<td>Left bundle branch block</td>
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<td>Ventricular tachycardia</td>
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<td>Ischemic cardiac events</td>
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Other chemotherapeutic agents such as mitoxantrone, cyclophosphamide, cisplatin, and 5-fluorouracil might cause CTX by inducing mitochondrial dysfunction, similar to that observed with anthracyclines. The toxic effect produced on mitochondria arises from an impairment of the respiratory chain, oxidative phosphorylation, Krebs cycle, or β-oxidation, with a consequent increase of oxidative stress, reduction of antioxidant capacity, and induction of apoptosis.38

**Drugs and mechanisms**

**Alkylating agents**

Cyclophosphamide at high doses causes structural injury to the heart and then permanent damage (type 1 CTX).36 This lesion develops as an acute myopericarditis and can cause cardiac tamponade and arrhythmias. The risk of CTX is dose-dependent and CTX occurs within 1 to 10 days after administration of the first dose of the drug.7–9 High-dose cyclophosphamide is associated with an increased risk of heart failure, ranging from 7 to 28%.10

The exact mechanism of cyclophosphamide-induced CTX is unknown. The drug can produce direct endothelial damage, followed by extravasation of toxic metabolites that damage myocytes, interstitial hemorrhage, and edema. Ischemic myocardial injury could be the result of intracapillary microemboli.3 Moreover, cyclophosphamide impairs cellular respiration and damages the inner mitochondrial membrane of cardiomyocytes, most likely through the induction of oxidative stress.4

Cyclophosphamide is converted to the unsaturated aldehyde acrolein, a toxic, reactive metabolite that induces extensive protein modification and myocardial injury. Thus, the role of glutathione S-transferase P (GSTP), an acrolein-metabolizing enzyme, in cyclophosphamide CTX has been investigated. The results showed that following cyclophosphamide treatment, GSTP insufficiency was associated with increased accumulation of protein-acrolein adducts in the heart; this suggests that cyclophosphamide CTX is regulated – at least partly – by GSTP, which prevents drug toxicity by metabolizing and detoxifying acrolein.5

High-dose ifosfamide has been associated with severe but reversible myocardial depression and malignant arrhythmias. Ifosfamide is similar to cyclophosphamide, and thus it might induce CTX through a mechanism similar to that of cyclophosphamide CTX. However, no histopathological evidence of hemorrhagic myocarditis was found in ifosfamide-treated patients.43

Recent data from an animal-model study showed that both cyclophosphamide and ifosfamide treatment inhibit the expression in cardiac tissues of the genes that encode heart fatty acid-binding protein and carnitine palmitoyltransferase I, and, consequently, inhibit mitochondrial transport and long-chain fatty acid oxidation. The results revealed a parallel progressive increase in serum lactate dehydrogenase, creatine kinase isoenzyme myocardial band, and malonyl-CoA content and the development of histopathological lesions in cardiac tissues, and thus confirmed a potential contribution of these pathways to cyclophosphamide and ifosfamide-induced CTX.6

**Platinum**

Cisplatin is a potent chemotherapeutic agent that exhibits broad-spectrum antineoplastic activity against diverse tumors. However, a major factor that limits cisplatin treatment is the drug’s acute and cumulative CTX, which includes ECG abnormalities, angina15 and acute myocardial infarction,16 hypertension17 and hypotension,18 arrhythmias, myocarditis, cardiomyopathy, and congestive heart failure.19 Platinum-based therapy has also been shown to increase the risk of thrombotic events in cancer patients.20

Cisplatin CTX can result either from a direct toxic action on cardiac myocytes or from reactive oxygen species (ROS) production, followed by the induction of oxidative stress and the switch to a prothrombotic condition.31 In an animal model, cisplatin induced a substantial increase in the plasma concentration of cardiac troponin I, which was associated with a marked increase in the malondialdehyde level, and, in parallel, a notable reduction in antioxidants (i.e. in glutathione content and superoxide dismutase activity) was observed; consequently, mitochondrial and nuclear DNA was heavily damaged.12 Another animal study revealed that cisplatin might lead to LV dysfunction and depressed cardiomyocyte contraction by inducing mitochondrial ultrastructural abnormalities, characterized by activation of the ER stress response and apoptosis.53

Platinum also induces platelet activation and aggregation, which potentially involves monocyte procoagulant activity and might alter endothelial cell integrity.14 Lastly, cisplatin might elevate the levels of von Willebrand factor, induce hypomagnesaemia and vasospasm, and trigger antiangiogenic activity.44–47

Cisplatin has been associated with a long-lasting profile of CTX, as reported in the case of survivors of testicular cancer,37 who showed an increased risk for myocardial infarction after treatment with cisplatin. In these patients, the plasma levels of cisplatin remain measurable for up to 20 years after completion of therapy and cause cumulative dysfunction of endothelial cells, which eventually detach from the vessel wall.48 Therefore, in this case, a long-lasting pharmacological signature (circulating cisplatin) correlates with molecular mechanisms of damage (endothelial dysfunction) and clinical events (myocardial infarction). Although circulating cisplatin is detectable in most of the survivors of testicular cancer, myocardial infarction occurs in 6% or fewer patients,49 which indicates high interpersonal variability in the response to cisplatin exposure.50
Antimetabolites
Cardiac toxicity of fluoropyrimidines is the second most common cause of chemotherapy-induced CTX. Most frequently, 5-fluorouracil causes angina-like chest pain; however, in rare cases, myocardial infarction, arrhythmias, ventricular tachycardia, heart failure and cardiogenic shock, and QT prolongation with torsades de pointes have been reported. The CTX incidence associated with 5-fluorouracil has been reported to vary from 1 to 68%. One prospective study determined that the incidence of capcitabine-associated CTX was 5.5%. A recent review assessed the CTX occurrence associated with 5-fluorouracil, capcitabine, or raltitrexed that was reported in articles published between January 1991 and August 2011; the finding was that the overall incidence of CTX associated with 5-fluorouracil/capcitabine varied between 0.55 and 19% (mean: 5.0%; median: 3.85%), but no CTX was associated with raltitrexed. Moreover, a meta-analysis reported an incidence of symptomatic CTX of 1.2 to 4.3% during treatment with 5-fluorouracil and suggested that the risk can be increased by continuous infusion and concurrent treatment with cisplatin.

The pathogenic mechanism of CTX associated with 5-fluorouracil and capcitabine is unknown; however, coronary thrombosis, arthritis, and vasospasm have been proposed as possible mechanisms. Certain metabolites of 5-fluorouracil, particularly α-fluoro-β-alanine, have been shown to be associated with CTX. Thymidine phosphorylase is an enzyme involved in the conversion of capcitabine into 5-fluorouracil and of 5-fluorouracil into its active metabolites; the enzyme is an angiogenic factor whose expression is upregulated in athero-sclerotic plaques and during myocardial infarction. Toxic effects of the drugs could also be caused through endothelial damage, with increased levels of endothelin 1 producing vasospasm and ischemia.

Additional hypothesized mechanisms of CTX are direct toxic effects of the drugs on the myocardium, interaction with the coagulation system, and autoimmune responses. A cardio-oncology study showed that 5-fluorouracil can induce apoptosis and autophagy through the production of oxidative stress in cardiomyocytes and endothelial cells. Moreover, Eskandari and colleagues conducted an animal-model study and demonstrated that the CTX resulting from 5-fluorouracil and capcitabine treatment was associated with the formation of ROS, lipid peroxidation, and a rapid depletion of glutathione; the resulting increase in oxidative stress was associated with mitochondrial dysfunction, which triggered caspase-3 activation and led to apoptosis or necrosis. Furthermore, 5-fluorouracil, but not capcitabine, caused lysosomal membrane leakage when incubated with cardiomyocytes. Conversely, studies on several animal models have suggested that another causative mechanism of CTX could be citrate accumulation in cardiomyocytes, attributed to the degradation of 5-fluorouracil into fluoro-acetate, which interferes with the Krebs cycle. Accordingly, other studies have shown that 5-fluorouracil can induce dose and time-dependent depletion of high-energy phosphates in myocardial cells.

Antibiotics
Mitoxantrone is a chemotherapeutic agent that can induce dose-dependent, irreversible CTX; the CTX risk is markedly increased after cumulative doses of at least 160 mg/m² of the drug. Mitoxantrone might induce arrhythmias, chronic heart failure, and persistent diastolic dysfunction in the absence of an impairment of LVEF. The mechanisms of mitoxantrone-associated CTX remain incompletely understood, but one suggested mechanism involves the formation of ROS in myocardial cells through interactions with cellular iron metabolism, which leads to tissue damage.

In an experimental animal model, mitoxantrone increased lactate levels and the activity of complexes IV and V of the mitochondrial respiratory chain, which underscores the role of mitochondriopathy in mitoxantrone-induced CTX. Moreover, a study conducted on H9c2 cells by using mitoxantrone at therapeutic concentrations showed that mitochondrial membrane potential and intracellular levels of ATP and calcium were changed; the authors concluded that the disruption of energy metabolism might be a key factor in mitoxantrone-induced cell damage.

Bleomycin use is associated with pericarditis and coronary artery disease. Serosal inflammation in the form of acute pleuropericarditis might be part of the generalized mucocutaneous toxicity that is common during bleomycin therapy. Conversely, ischemic cardiomyopathy could be caused by the toxic and inflammatory effects of bleomycin on endothelial cells. Ultimately, this chemotherapy-induced cellular activation can progress to endothelial dysfunction, accelerated atherosclerosis, and overt CVD.

Notably, in patients with testicular cancer, myocardial infarction has been reported to potentially occur after a single dose of bleomycin, as well as years after completion of cumulative bleomycin regimens. Moreover, mitomycin C might lead to chronic heart failure, with the risk being increased after cumulative doses of at least 30 mg/m².

Lastly, drugs belonging to this class might potentially induce cardiac damage through pathways related to an increase in oxidative stress, although by mechanisms that differ from those of anthracyclines.

Antimicrotubule agents (paclitaxel and docetaxel)
In 5% of patients treated with paclitaxel, atrioventricular block, left bundle branch block, ventricular tachycardia,
and ischemic cardiac events were observed, whereas asymptomatic bradycardia occurred in a variable proportion of patients (from <0.1 to 31%).\(^\text{33}\) Arrhythmias and conduction disorders were suggested to be potentially caused by the effects of paclitaxel on the Purkinje system or extracardiac autonomic control.\(^\text{35}\) After these adverse cardiac events were observed during the monitoring of patients, which was justified by the high incidence of serious hypersensitivity reactions induced by paclitaxel in phase I studies, clinical trials have excluded patients with a diagnosed heart disease and patients under any medication that could interfere with cardiac conduction.\(^\text{20}\)

Among all antimicrotubule agents in clinical use, paclitaxel is formulated with the highest concentration per dose of Cremophor EL, which is recognized to induce the release of histamine; the released histamine, in turn, stimulates its specific cardiac receptors and increases the oxygen demand of the myocardium, and might lead to coronary vasoconstriction and chronotropic consequences.\(^\text{33}\) These effects, even in distinct combinations, might be responsible for the induction of myocardial ischemia observed in patients receiving paclitaxel treatment.\(^\text{20,33}\) Notably, paclitaxel, but not docetaxel, is able to delay the catabolism of doxorubicin, thus leading to a higher incidence, although not statistically significant, of reduction in LVEF.\(^\text{34,64}\)

The incidence of docetaxel-associated heart failure has been documented to range from 1.6 to 2%,\(^\text{65,66}\) but the incidence of myocardial ischemia has been reported only in the drug’s package insert (http://products.sanofi.us/Taxotere/taxotere.html). Notably, congestive heart failure has been observed in metastatic breast cancer patients who received prior adjuvant anthracycline therapy and when docetaxel was combined with trastuzumab treatment for human epidermal growth factor receptor 2-positive disease.\(^\text{66}\) Asymptomatic reductions in LVEF of at least 15% have been reported in 6–8% of the patients treated with docetaxel.\(^\text{56,67}\) this percentage is higher in patients pretreated with anthracycline and in those who received the trastuzumab–docetaxel combination for human epidermal growth factor receptor 2-positive metastatic breast cancer.\(^\text{66}\)

**Conclusion**

The complex and heterogeneous mechanism of CTX, the large variability in the time of onset of cardiac injury, and the extremely variable clinical presentation – or even asymptomatic occurrence – of damages warrant an extensive cautionary cardiac surveillance of all cancer patients undergoing antineoplastic treatments. Specifically, we must deepen our knowledge of the incidence, mechanisms, and potential therapeutic targets of CTX induced by various nonanthracycline chemotherapeutic agents.\(^\text{68}\)

Despite this background, the CTX induced by nonanthracycline chemotherapy is pleomorphic and remains poorly predictable; moreover, the mechanisms of CTX can be established with certainty only in a few cases. Accordingly, treatment with only a few nonanthracycline chemotherapeutic agents, such as mitoxantrone, mitomycin, and ifosfamide, leads to CTX in a recognizable dose and schedule-dependent manner.

In the absence of detailed information, for nonanthracyline chemotherapy drugs, the overall concept that applies is that preexisting comorbidities such as hypertension, diabetes, and hyperlipidemia, or unfavorable lifestyle choices such as reduced physical activity increase the risk of CTX.\(^\text{69}\) Consequently, asymptomatic, potentially reversible CTX resulting from ‘well tolerated doses’ of nonanthracycline chemotherapeutics might progress to symptomatic events by overlapping with other risk factors, according to the hypothesis that late-onset CTX builds on pharmacologic and nonpharmacologic sequential injuries.

In clinical practice, patients are typically treated with multiple, consecutive lines of chemotherapy regimens. Therefore, the possibility of a reciprocating interaction between drugs of distinct classes must be accounted for, as in the cases of patients undergoing a cycle of anthracycline treatment in combination with nonanthracycline chemotherapy. The knowledge that oncologists and cardiologists gain regarding the pathophysiology of CTX induced by individual chemotherapeutic agents will help in improving the identification of the risk profile of each patient and in the planning of a preventive strategy that is as tailored as possible.

**Acknowledgement**

There are no conflicts of interest.

**References**


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