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Chemotherapy-Induced Cardiotoxicity in Breast and Haematological Cancers: A Comprehensive Review

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Abstract

In recent years, chemotherapeutic regimens have advanced with great success that has enhanced survival rates in patients with breast and haematological malignancies. Nevertheless, the rising life expectancy among cancer patients has made long-term adverse effects of the treatment more prominent, and cardiotoxicity is one of the leading causes of morbidity and mortality.

Cardiotoxicity caused by chemotherapy involves a continuum of structural and functional cardiac pressures that comprise of left ventricular dysfunction (asymptomatic), left ventricular dysfunction (symptomatic), heart failure (overt), arrhythmias, ischemic heart disease, and cardiomyopathy. The cardiotoxic risk is specifically linked with breast cancer and haematological malignancies, as anthracyclines, HER2-targeted therapy, alkylating therapy use, and the use of more recent targeted and immune-based therapy are common. This review is a comprehensive and clinically structured review on the mechanisms, risk factors, clinical manifestation, diagnostic interventions, and treatment of chemotherapy-induced cardiotoxicity in breast and haematological malignancies. The focus is made on early detection and preventive measures as well as the growing role of clinical pharmacists as a part of multidisciplinary cardio-oncology care. These points are important to understand how to maximize the oncologic outcomes with the minimal cardiovascular problems.

Keywords: Chemotherapy-induced cardiotoxicity, Breast cancer, Haematological malignancies , Anthracyclines, HER2-targeted therapy, Cardio-oncology, Left ventricular dysfunction.

1. Introduction

Breast cancer and haematological malignancies are among the most common cancers worldwide, and chemotherapy plays a major role in their treatment. Advances in chemotherapy have improved survival rates; however, these treatments can also cause serious adverse effects. One important complication is chemotherapy-induced cardiotoxicity, which affects the structure and function of the heart.

Cardiotoxicity may lead to conditions such as arrhythmias, cardiomyopathy, and heart failure, either during treatment or long after therapy. Early detection, monitoring, and proper management are important to reduce these complications. The field of cardio-oncology focuses on preventing and managing cardiovascular problems in cancer patients, where clinical pharmacists also play a key role in optimizing therapy and ensuring patient safety.

1.1 Epidemiology of Breast and Haematological Cancers

The breast cancer is the most widely diagnosed cancer among women in the world, as it imposes significant cancer morbidity and mortality rates. At the same time, haematological malignancies such as leukemias, lymphomas, multiple myeloma, are a heterogeneous group of malignancies whose incidence is increasing as a result of the development of better diagnostic tools and an ageing population. The popularity of combination chemotherapy, targeted therapy and immunotherapy have significantly advanced the survival rates in the two types of diseases. As a result, an increasing number of long-term cancer patients are currently exposed to long-lasting and delayed unwanted effects of anticancer therapies, with cardiovascular toxicity being one of major clinical concern. [11]

1.2 Evolution of the Chemotherapy and Survival Rates.

The advent of anthracyclines transformed the treatment of cancer by providing high antitumor effects in several cancers[8].Later developments, such as monoclonal antibodies, tyrosine kinase inhibitors, and immune checkpoint inhibitors, added further to the precision of the therapy and survival rates. Although these treatments have revolutionized cancer treatment, a major drawback has been realized through their cardiotoxic effect.

Long term cardiac surveillance is imperative as better survival has revealed the revelation of late onset cardiovascular complications which can be present several or even many years after the end of treatment.

1.3 The origin of Chemotherapy-induced Cardiotoxicity.

Cancer survivors are now known to experience cardiotoxicity induced by chemotherapy as one of the major causes of non-cancer related morbidity and mortality[3]. Clinical manifestation is varied, and it may be subclinical injury that only manifests itself in biomarkers or images or progression of heart failure with severe functional deficits. Notably, cardiotoxicity can require the shutdown or halting of potentially life-saving chemotherapy, which has a negative impact on oncologic outcomes. This two-fold effect emphasizes the significance of balancing the safety of the cardiovascular against the control of cancer.

1.4 Clinical Pharmacist Role in Cardio-Oncology.

The growing complexity around the treatment of cancer has made clinical pharmacists a part and parcel of the cardio-oncology team. Pharmacists are crucial in screening at-risk patients, optimization of drug dose, interplay, cardiotoxic biomarker, and patient education about cardiovascular risk factors. They are especially relevant in the breast and haematological cancer with polypharmacy and cumulative exposure to cardiotoxic effects being frequent. The pharmacist- led initiative can play an important role in the early identification and prevention of heart complications. **[3]**

2. Introduction to Chemotherapy-Induced Cardiotoxicity

2.1 Definition and clinical Classification

Also known as cancer therapy-related cardiac dysfunction (CTRCD), chemotherapy-induced cardiotoxicity is any structural or functional heart damage that may be caused by anticancer treatment. The European Society of Cardiology has established CTRCD mainly through a decrease in the left ventricular ejection fraction with clinical symptoms or without any symptoms.

Nonetheless, cardiotoxicity is not confined to systolic dysfunction, and may include diastolic dysfunction, arrhythmias, ischemia, hypertension and pericardial disease.[1][2][3]

2.2 Acute, Subacute and Chronic Cardiotoxicity.

Depending on the onset time cardiotoxicity is typically characterized as acute, early-onset and late- onset cardiotoxicity.

Acute cardiotoxicity: This is a reversible condition that happens in the course of or shortly after chemotherapy (acute cardiotoxicity) and may be transient arrhythmias or an ECG abnormality. Cardiotoxicity occurs early in treatment usually in the first year of treatment and can result in symptomatic heart failure. The late-onset cardiotoxicity may ensue many years following drug discontinuation and is often irreversible especially in patients who received large cumulative doses of anthracyclines during childhood or at an early age. [3,8]

2.3 Reversible and Irreversible Cardiac Damages.

A significant clinical difference concerning cardiotoxicity is reversible and irreversible myocardial injury. Anthracyclines are classically linked with type I cardiotoxicity, where the cardiomyocytes are permanently damaged with cardiomyocyte loss at the dose. Conversely, Type II cardiotoxicity, which is typically associated with HER2-targeted therapy, manifests itself with myocardial dysfunction and is not accompanied by structural damage and is typically reversible when treatment is stopped. This difference is important to therapeutic decision-making and patient management in the long term.

3. Pathophysiology of Chemotherapy-induced Cardiotoxicity.

Cardiotoxicity that occurs due to chemotherapy is a multidimensional mechanism that entails intricate molecular, cellular, and structural changes that occur in the myocardium. The mechanisms differ with the chemotherapeutic agent, cumulative dose, susceptibility of the patient and the presence of underlying cardiovascular disease. In spite of these differences, some common causative mechanisms result in myocardial damage, which eventually leads to functional deficiency.

Oxidative Stress and Free Radical Injury Oxidative stress and free radical injury are the third and fourth stages of cellular damage.

3.1 Oxidative Stress and Free Radical Injury

Among the most researched mechanisms leading to anthracycline-induced cardiotoxicity, oxidative stress must be mentioned. These agents are redox cycled in the cardiomyocytes thereby causing excessive production of reactive oxygen species (ROS). The cardiac system is singularly susceptible to oxidative damage owing to an elevated level of mitochondria as well as comparatively restricted antioxidant defenses. The overproduction of ROS leads to destruction of cell lipids, proteins and nucleic acid, which causes impaired contractility of the myocardial cells and eventual death of cardiomyocytes.

Persistent oxidative stress fosters cumulative myocardial damage in breast and haematological cancer patients who are put through repeated chemotherapy cycles. [1,8]

This is a dose-dependent process which is highly associated with the long-term dysfunction of the heart. Notably, oxidative damage can also linger upon the termination of chemotherapy, which is the cause of delayed cardiotoxicity in cancer survivors.

3.2 Mitochondrial Sarcomyosis and Energy Depletion.

Mitochondria serve as the main factors in the operation of energy synthesis and survival of the cells in the heart. A number of chemotherapeutic agents destabilize the structure and functioning of mitochondria resulting in the disruption of oxidative phosphorylation and loss of adenosine triphosphate (ATP). Precisely anthracyclines are localized in the mitochondria and disrupt the action of the electron transport chain leading to additional generation of ROS and destruction of mitochondrial DNA.

Mitochondrial dysfunction impairs cardiomyocyte energy metabolism which limits the capacity of the heart to adjust to physiological stress. In the long run, this energy deprivation leads to myocardial remodelling, decrease in contractile reserve and subsequent heart failure. In haematological malignancies,

high doses of chemotherapy regime and conditioning regimens of transplanting stem cell transplantation worsens mitochondrial damage further and poses the risk of irreversible cardiac damage. [1]

3.3 Calcium imbalance/apoptosis Myocytes Apoptosis

Normal cardiac excitation-contraction coupling requires calcium homeostasis. Calcium is affected by chemotherapeutic agents which modify the sarcoplasmic reticulum functions and the activity of calcium channels. High intracellular accumulation of calcium induces the opening of mitochondrial permeability transition pore causing the loss of membrane potential and the activation of apoptotic pathways.

Apoptosis is one of the important mechanisms of cardiomyocyte damage during chemotherapy- induced cardiotoxicity. In contrast to necrosis, apoptotic cell death proceeds in a controlled fashion but leads to a gradual process of viable myocardial tissue loss. Since cardiomyocytes have a limited regenerative ability, progressive apoptosis will result in the ventricular thinning, dilation and systolic dysfunction. The mechanism is especially applicable in long term cardiotoxicity, which is linked to anthracycline exposure. [13]

3.4 Inflammatory and Endothelial Pathways

The endothelial mechanism involves inflammatory pathways that are triggered by diverse external factors such as infections, injuries, infections, trauma, and irradiation (Loot et al., 2012).

The role that inflammation plays in chemotherapy-related cardiac injury is becoming even more popular. Some of the chemotherapeutic drugs stimulate the production of pro-inflammatory cytokines, enhancing endothelial dysfunction and microvascular damage. The damage of endothelia impairs coronary microcirculation, which decreases the supply of oxygen to the myocardium and increases ischemic stress. Endothelial dysfunction is also known to cause hypertension, thrombosis, and accelerated atherosclerosis in cancer survivors. Oxidative stress can work in combination with inflammatory pathways in synergizing myocardial injury in breast cancer patients who undergo targeted therapies. The mechanisms underscore the systemic character of cardiovascular risk that is associated with chemotherapy-induced cardiotoxicity and the necessity of extensive cardiovascular risk management.

4. Cardiotoxic Chemotherapeutic Agents

A wide range of chemotherapeutic and targeted agents used in breast and haematological cancers are associated with varying degrees of cardiotoxicity. The risk is influenced by cumulative dose, treatment duration, combination regimens, and individual patient factors.

4.1 Anthracyclines

Anthracycline-induced cardiotoxicity in both breast and hematological cancers is primarily driven by oxidative stress and excessive free-radical generation. Anthracyclines undergo redox cycling in cardiomyocytes, producing reactive oxygen species such as superoxide anions, hydrogen peroxide, and hydroxyl radicals. The heart is particularly vulnerable because of its low antioxidant defenses (reduced catalase and glutathione peroxidase activity) and high mitochondrial density, leading to lipid peroxidation, protein oxidation, and DNA damage. In addition, anthracyclines inhibit topoisomerase IIβ (Top2β) in cardiomyocytes, causing double-stranded DNA breaks and activation of p53-mediated apoptosis, resulting in irreversible loss of cardiomyocytes and dose-dependent permanent damage. Mitochondrial accumulation of anthracyclines further impairs mitochondrial DNA and the electron transport chain, leading to ATP depletion, increased ROS, mitochondrial permeability transition pore opening, and cardiomyocyte apoptosis or necrosis. Iron-anthracycline complex formation amplifies toxicity by enhancing Fenton reactions, generating highly reactive hydroxyl radicals that exacerbate myocardial

injury. [1,8,13]

4.2 HER2-Targeted Therapies

HER2-targeted therapies used in breast cancer, particularly trastuzumab and pertuzumab, are associated with Type II cardiotoxicity, which is mechanistically distinct from anthracycline-induced injury. In cardiomyocytes, HER2 signaling is crucial for cell survival, repair mechanisms, and adaptation to physiological stress, largely through its interaction with neuregulin-1 and downstream activation of the PI3K/Akt and MAPK signaling pathways. Trastuzumab-mediated HER2 inhibition disrupts these survival pathways, leading to impaired stress responses, increased susceptibility to oxidative damage, reduced myocardial contractility, and reversible cardiac dysfunction. Cardiotoxicity is markedly amplified when HER2-targeted therapy is combined with anthracyclines, as prior anthracycline-induced myocardial injury coupled with HER2 blockade prevents effective cardiac repair, significantly increasing the risk of heart failure. Additionally, in patients with pre-existing cardiovascular disease, alkylating agent–induced cardiotoxicity may further contribute to cardiac dysfunction, compounding overall cardiovascular risk.

4.3 Alkylating Agents

One abnormality caused by alkylating agents is cardiotoxicity caused by direct cytotoxic actions on cardiomyocytes and vascular endothelial cells. These medications create cross-links with DNA, which will result in blocking the replication of the DNA and activate apoptotic processes in the heart cells. Alkylating agent metabolites (cyclophosphamide-derived acrolein, in particular cause too much of reactive oxygen species, which leads to oxidative stress and lipid peroxidation Of cardiomyocyte membranes.

Alkylating agents induce endothelial damage that elevates the capillary permeability resulting in interstitial myocardial edema and microvascular dysfunction. The impairment of the myocardial microcirculation is followed by myocardial haemorrhage, fibrin deposition, and the inflammatory involvement of cells that further undermines the cardiac structure and functioning. Oxidative stress and inflammatory mediators interfere with the integrity of mitochondria, impede the ATP production, and favor necrosis of cardiomyocytes.

Also, alkylating agents encourage the pro-inflammatory cytokines and endothelial adhesion molecules, which helps in myocardial inflammation and fibrosis. The end result of these mechanisms is impaired myocardial contractility, diastolic dysfunction, arrhythmogenesis, and acute heart failure, especially when the cumulative dose is high. [3]

4.4 Antimetabolites

Antimetabolite-induced cardiotoxicity occurs mainly due to direct myocardial injury, endothelial dysfunction, and coronary vasospasm, and is most commonly associated with agents such as 5-fluorouracil (5-FU), capecitabine, cytarabine, and methotrexate. These drugs interfere with nucleic acid synthesis and cellular metabolism, which in cardiomyocytes leads to mitochondrial dysfunction, ATP depletion, and increased oxidative stress.

Fluoropyrimidines (5-FU and capecitabine) are strongly linked to coronary vasospasm and endothelial damage, causing reduced nitric oxide production, increased endothelin-1 release, and transient myocardial ischemia that may manifest as angina, arrhythmias, or myocardial infarction. Antimetabolites also promote direct cardiomyocyte apoptosis, inflammation, and microvascular thrombosis, further impairing myocardial perfusion. Collectively, these mechanisms result in reversible or irreversible cardiac dysfunction, particularly in patients with underlying cardiovascular disease or concurrent exposure to other cardiotoxic chemotherapeutic agents. [3,9]

4.5 Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKIs) are associated with cardiotoxicity primarily because of their accidental activity in the support of the kinases that are essential to the maintenance of cardiomyocytes, mitochondrial and blood vessel stability. Many TKIs interfere with signaling pathways, such as PI3K/Akt, AMPK and MAPK, which are essential to cellular regulation of heart muscle contraction and cellular energy balance. Blocking such pathways leads to the dysfunction of the mitochondria, the diminished ATP synthesis, and the increased oxidative stress in the myocytes.

TKIs also cause endothelial dysfunction via the impairment of signal transduction of vascular endothelial growth factor (VEGF) which lowers the supply of nitric oxide and increases vascular rigidity. The destruction of endothelial cells contributes to systemic hypertension, microvascular ischemia, and augmented cardiac afterload and escalates the load to the myocardium. Other TKIs accelerate the onset of atherosclerosis and thrombotic occurrences by worsening platelet activation and inflammation in blood vessels.

Also, tyrosine kinase inhibitors can trigger the process of apoptosis in cardiomyocytes, disrupt the regulation of autophagy, which leads to the progressive destruction of the myocardium and the ventricular remodelling. TKIs have long-term outcomes including left ventricular systolic dysfunction, heart failure, arrhythmias as well as ischemic heart events, albeit in different severities depending on the selectivity of the drug, dosage, and duration of use. Cardiotoxicity Induced by Proteasome Inhibitor.

4.6 Cardiotoxicity was induced by protease inhibitors

Proteasome inhibitors also stimulate cardiotoxicity through destabilizing the ubiquin-proteasome system that plays a vital role in ensuring homeostasis of cardiac muscle cells. Proteasomal inhibition causes the accumulation of misfolded and damaged proteins, which causes endoplasmic reticulum stress and activation of the unfolded protein response. Constant cell stress will initiate dysfunction of the mitochondria, amplified oxidative stress, and apoptosis of cardiomyocytes. [9]

Proteasome inhibitors also provoke the deterioration of calcium-handling and contractile protein degradation, which cause the decrease of myocardial contractility. Moreover, these agents disrupt nitric oxide signaling and endothelial activity leading to vascular dysfunction and the rise in systemic vascular resistance. This causes an imbalance in the supply and demand of Myocardial oxygen which also adds to the cause of cardiac injury.

Moreover, the inhibition of proteasomes triggers the pro-inflammatory activities and fibrotic signatures, which favor myocardial inflammation and interstitial fibrosis. These interconnected processes eventually cause left ventricular dysfunction, heart failure, hypertension, ischemic events, and arrhythmias with cardiotoxicity being greater with second-generation agents like carfilzomib than first-generation proteasome inhibitors.

4.7 Dose-Dependent versus Dose-Independent Toxicity

Understanding whether cardiotoxicity is dose-dependent or dose-independent has important clinical implications. Dose-dependent cardiotoxicity, as seen with anthracyclines, emphasizes the need for cumulative dose tracking and dose-limiting strategies. Dose-independent toxicity, associated with targeted and immune therapies, requires vigilant monitoring regardless of exposure duration.

Tailoring surveillance and preventive strategies based on the specific agent is essential for optimal patient care.

5. Chemotherapy-Induced Cardiotoxicity in Breast Cancer

Breast cancer treatment has evolved into a multimodal approach incorporating surgery, radiotherapy, chemotherapy, targeted therapy, and hormonal agents. While these advances have substantially improved survival, they have also increased the burden of treatment-related cardiovascular complications. Cardiotoxicity in breast cancer patients is particularly relevant due to the frequent use of anthracyclines and HER2-targeted therapies, often administered sequentially or in combination

5.1 Common Treatment Regimens and Cardiac Risk

Anthracycline-based regimens remain widely used in both early-stage and metastatic breast cancer. These regimens are associated with a well-documented risk of dose-dependent cardiomyopathy. The introduction of HER2-targeted therapies has further complicated the cardiovascular risk profile, as these agents interfere with cardioprotective signaling pathways.

Sequential administration of anthracyclines followed by HER2-targeted therapy significantly increases the likelihood of left ventricular dysfunction compared to either agent alone. Additionally, the use of combination regimens and dose-dense protocols may amplify cardiotoxic risk, particularly in patients with pre-existing cardiovascular disease or advanced age. [3,9]

5.2 Incidence and Severity Patterns

The reported incidence of cardiotoxicity in breast cancer varies widely depending on diagnostic criteria, duration of follow-up, and patient population. Asymptomatic reductions in left ventricular ejection fraction are more common than overt heart failure and may go undetected without systematic monitoring. However, even subclinical dysfunction has been associated with an increased risk of future cardiovascular events.

Severity patterns differ based on treatment exposure. Anthracycline-related cardiotoxicity often presents as a progressive decline in systolic function, whereas HER2-targeted therapy typically results in reversible myocardial dysfunction. Importantly, repeated episodes of transient dysfunction may predispose patients to long-term cardiac impairment. [2]

5.3 Clinical Outcomes and Prognostic Implication.

Cardiotoxicity has significant implications for both cancer-related and overall survival in breast cancer patients. Development of cardiac dysfunction may necessitate treatment interruption, dose reduction, or discontinuation of effective anticancer therapy, potentially compromising oncologic outcomes. Furthermore, cardiovascular complications contribute substantially to long-term morbidity among breast cancer survivors.

Early identification and timely management of cardiotoxicity can improve cardiac outcomes and allow continuation of cancer therapy in many cases. This highlights the importance of integrated cardio-oncology care pathways in breast cancer management. [2,3]

6. Chemotherapy-Induced Cardiotoxicity in Haematological Malignancies

Haematological malignancies encompass a diverse group of cancers requiring intensive and often prolonged chemotherapy. Patients with these malignancies are exposed to high cumulative doses of cardiotoxic agents, making them particularly vulnerable to both acute and chronic cardiac complications.

6.1 Standard Chemotherapy Protocols

Anthracyclines are integral to many standard treatment protocols for haematological malignancies. Their cardiotoxic effects are well recognized and may manifest during treatment or years later. In addition to anthracyclines, alkylating agents and antimetabolites contribute to the overall cardiotoxic burden in these

patients.

The use of combination regimens increases the complexity of cardiotoxic risk assessment. Overlapping toxicities and cumulative exposure necessitate careful monitoring throughout the treatment course and beyond.

6.2 High-Dose Chemotherapy and Transplant-Related Cardiotoxicity

High-dose chemotherapy followed by hematopoietic stem cell transplantation represents a curative strategy for several haematological malignancies. However, the conditioning regimens used in transplantation are associated with substantial cardiotoxic risk. Acute complications may include arrhythmias, myocarditis, and pericardial disease, while chronic effects include restrictive cardiomyopathy and heart failure. [3]

Transplant survivors require long-term cardiac surveillance due to the potential for delayed cardiotoxicity. The presence of pre-transplant cardiovascular risk factors further increases susceptibility to adverse outcomes.

6.3 Long-Term Cardiac Sequelae in Survivors

Improved survival in haematological malignancies has led to an expanding population of long-term survivors with significant cardiovascular morbidity. Late-onset cardiotoxicity may manifest decades after treatment, particularly in patients treated during childhood or adolescence.

These long-term sequelae underscore the need for lifelong cardiovascular follow-up and risk factor modification. Early intervention may mitigate progression to symptomatic heart disease and improve quality of life. [2,3]

7. Risk Factors for Chemotherapy-Induced Cardiotoxicity

The development of cardiotoxicity is influenced by a complex interplay of patient-related, treatment-related, and genetic factors. Identification of high-risk individuals is essential for implementing targeted preventive and monitoring strategies.

7.1 Patient-Related Risk Factors

Advanced age is a well-established risk factor for chemotherapy-induced cardiotoxicity, reflecting age-related decline in cardiac reserve and increased prevalence of comorbidities. Pre-existing cardiovascular disease, hypertension, diabetes mellitus, and obesity further increase susceptibility to myocardial injury.

Female sex has been associated with increased risk in certain contexts, although this may be confounded by disease-specific treatment patterns. Lifestyle factors such as smoking and physical inactivity also contribute to overall cardiovascular risk.

7.2 Treatment-Related Risk Factors

Cumulative dose, infusion rate, and treatment duration are critical determinants of cardiotoxic risk. Combination therapy with multiple cardiotoxic agents amplifies myocardial injury. Concurrent radiotherapy involving the chest further increases the likelihood of cardiovascular complications through additive endothelial and myocardial damage.

Repeated exposure to cardiotoxic chemotherapy, particularly in relapsed or refractory disease, compounds long-term cardiac risk and necessitates vigilant surveillance. [3]

7.3 Drug–Drug Interactions and Polypharmacy

Polypharmacy is common in cancer patients, especially those with comorbid conditions. Drug–drug interactions may potentiate cardiotoxic effects by altering pharmacokinetics or pharmacodynamics. For example, concomitant use of medications that prolong the QT interval may increase the risk of arrhythmias

when combined with certain chemotherapeutic agents.

Clinical pharmacists play a crucial role in identifying and managing potential interactions, adjusting therapy as needed to minimize cardiovascular risk.

7.4 Pharmacogenomic Considerations

Genetic variability influences individual susceptibility to chemotherapy-induced cardiotoxicity. Polymorphisms affecting drug metabolism, oxidative stress pathways, and myocardial repair mechanisms have been associated with differential risk. While pharmacogenomic testing is not yet routine in clinical practice, emerging evidence suggests it may enable more personalized risk stratification in the future. [13]

8. Clinical Presentation and Diagnosis of Chemotherapy- Induced Cardiotoxicity

The clinical presentation of chemotherapy-induced cardiotoxicity is highly variable and depends on the type of chemotherapeutic agent, duration of exposure, and individual patient susceptibility. Cardiac involvement may remain asymptomatic for prolonged periods or progress rapidly to severe, life-threatening complications. Early recognition is essential to prevent irreversible myocardial damage and optimize both cardiovascular and oncologic outcomes.

8.1 Clinical Signs and Symptoms

Patients may present with a wide spectrum of symptoms ranging from mild fatigue and exertional dyspnea to overt signs of heart failure such as orthopnea, peripheral edema, and paroxysmal nocturnal dyspnea. Palpitations, chest pain, and syncope may indicate arrhythmias or ischemic events. Importantly, a significant proportion of patients remain asymptomatic despite measurable cardiac dysfunction, underscoring the limitation of symptom-based detection alone.

In breast and haematological cancer patients, symptoms are often nonspecific and may overlap with chemotherapy-related fatigue, anemia, or pulmonary toxicity. This overlap can delay diagnosis unless proactive monitoring strategies are implemented.

8.2 Electrocardiographic Abnormalities

Electrocardiography (ECG) serves as a readily accessible tool for the initial evaluation of cardiac electrical disturbances. Common ECG findings associated with chemotherapy-induced cardiotoxicity include sinus tachycardia, QT interval prolongation, atrial and ventricular arrhythmias, and nonspecific ST–T wave changes.While ECG abnormalities may be transient, persistent changes warrant further investigation. QT prolongation is of particular concern due to its association with malignant ventricular arrhythmias, especially in patients receiving tyrosine kinase inhibitors or agents that alter electrolyte balance.

8.3 Echocardiography and Advanced Cardiac Imaging

Echocardiography remains the cornerstone of cardiac imaging in patients receiving potentially cardiotoxic chemotherapy. Measurement of left ventricular ejection fraction (LVEF) provides a standardized assessment of systolic function and is widely used to define cancer therapy-related cardiac dysfunction. However, reductions in LVEF often occur late in the disease process, after significant myocardial injury has already developed.

Advanced echocardiographic techniques, such as global longitudinal strain (GLS), allow detection of subtle myocardial dysfunction before overt changes in LVEF occur.

A relative reduction in GLS has emerged as a sensitive marker of early cardiotoxicity and is increasingly incorporated into surveillance protocols.Cardiac magnetic resonance imaging offers superior tissue characterization and enables detection of myocardial fibrosis, inflammation, and edema. Although less widely available, it is particularly useful in complex cases or when echocardiographic findings are

inconclusive. [2]

8.4 Role of Cardiac Biomarkers

Cardiac biomarkers play a critical role in the early detection of myocardial injury. Elevations in cardiac troponins reflect cardiomyocyte damage and have been associated with an increased risk of subsequent left ventricular dysfunction. Serial measurement of troponins during chemotherapy can identify patients at high risk for cardiotoxicity even in the absence of clinical symptoms.

Natriuretic peptides, including B-type natriuretic peptide (BNP), provide additional information regarding myocardial stress and volume overload. While less specific than troponins, elevated levels may signal early hemodynamic compromise. Integration of biomarkers with imaging enhances risk stratification and informs clinical decision-making. [2]

9. Monitoring and Surveillance Strategies

Systematic monitoring and surveillance are central to minimizing the impact of chemotherapy- induced cardiotoxicity. Evidence-based surveillance protocols aim to detect early myocardial injury, guide therapeutic interventions, and allow safe continuation of cancer therapy whenever possible.

9.1 Baseline Cardiac Assessment

A comprehensive baseline cardiac evaluation is essential prior to initiation of potentially cardiotoxic chemotherapy. This assessment typically includes a detailed cardiovascular history, physical examination, ECG, and echocardiography. Identification of pre-existing cardiovascular disease or risk factors allows individualized risk stratification and informs treatment planning.

Baseline measurement of cardiac biomarkers may provide additional prognostic information, particularly in high-risk patients. Establishing baseline values facilitates interpretation of subsequent changes during therapy.

9.2 On-Therapy Monitoring Protocols

During chemotherapy, periodic cardiac monitoring enables early detection of subclinical cardiotoxicity. The frequency and intensity of monitoring depend on the specific agent, cumulative dose, and patient risk profile. Anthracycline-based regimens often require more intensive surveillance due to their dose-dependent cardiotoxicity.

Serial echocardiography and biomarker assessment are commonly employed during treatment. Detection of early abnormalities may prompt initiation of cardioprotective therapy or modification of chemotherapy dosing, potentially preventing progression to overt heart failure. [2]

9.3 Post-Chemotherapy Follow-Up

Cardiotoxic effects may emerge long after completion of cancer therapy, particularly in patients treated with anthracyclines or high-dose chemotherapy. Long-term follow-up is therefore essential, especially in childhood cancer survivors and patients undergoing stem cell transplantation.

Post-treatment surveillance strategies should be tailored to individual risk profiles and may extend for several years or even lifelong in high-risk populations. Continued monitoring enables timely intervention and improves long-term cardiovascular outcomes. [3]

9.4 Pharmacist-Led Monitoring Models

Clinical pharmacists play an increasingly important role in monitoring and surveillance programs. Pharmacist-led initiatives may include medication review, dose optimization, identification of drug– drug interactions, and coordination of cardiac testing. Pharmacists also contribute to patient education, promoting adherence to monitoring schedules and lifestyle modifications. Integration of pharmacists into

cardio-oncology teams enhances continuity of care and supports early detection of cardiotoxicity, particularly in resource-limited settings.

10. Prevention and Risk Reduction Strategies

Prevention of chemotherapy-induced cardiotoxicity is a critical component of modern oncology care. Given that myocardial injury may be irreversible once clinically apparent, preventive strategies focus on minimizing cardiac exposure to toxic agents, identifying high-risk patients early, and implementing cardioprotective interventions.

10.1 Dose Optimization and Scheduling

Cumulative dose limitation remains one of the most effective strategies for reducing cardiotoxic risk, particularly with anthracyclines. Alternative dosing schedules, such as continuous infusion or lower peak doses, have been shown to reduce myocardial exposure and oxidative stress. In selected patients, substitution with less cardiotoxic agents or liposomal formulations may further reduce risk without compromising oncologic efficacy.

10.2 Cardioprotective Agents

Pharmacological cardioprotection has emerged as an important preventive strategy. Agents such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers have demonstrated benefit in preserving left ventricular function when initiated early in patients at risk. These agents reduce myocardial workload, limit remodeling, and counteract neurohormonal activation. [8]

Dexrazoxane has shown efficacy in reducing anthracycline-induced cardiotoxicity by chelating iron and limiting free radical formation. Its use is generally reserved for patients receiving high cumulative anthracycline doses due to concerns regarding potential interference with anticancer efficacy.

10.3 Supportive Care and Lifestyle Modification

Optimization of cardiovascular risk factors plays a complementary role in cardiotoxicity prevention. Blood pressure control, glycemic management, smoking cessation, and promotion of physical activity contribute to overall cardiovascular resilience. Patient education regarding early cardiac symptoms enhances prompt reporting and intervention.

11. Management of Established Chemotherapy-Induced Cardiotoxicity

Management strategies aim to stabilize cardiac function, prevent progression, and enable continuation of effective cancer therapy whenever feasible.

11.1 Pharmacological Management

Standard heart failure therapies form the cornerstone of treatment for chemotherapy-induced cardiac dysfunction. Early initiation of guideline-directed medical therapy has been associated with partial or complete recovery of cardiac function in a subset of patients, particularly when dysfunction is detected early.

Arrhythmias are managed according to standard cardiology guidelines, with careful consideration of drug–drug interactions and QT-prolonging potential of concurrent chemotherapy. [2,3]

11.2 Modification or Discontinuation of Chemotherapy

In cases of significant cardiotoxicity, modification of chemotherapy dosing or temporary interruption may be necessary. Decisions must balance the severity of cardiac dysfunction against the urgency of cancer control. Rechallenge with cardiotoxic agents may be considered in selected cases under close cardiac monitoring.

11.3 Multidisciplinary Cardio-Oncology Approach

Collaborative care involving oncologists, cardiologists, and pharmacists is essential for optimal management. Multidisciplinary decision-making allows individualized treatment plans that address both oncologic and cardiovascular priorities.

11.4 Role of the Clinical Pharmacist in Therapy Optimization

Clinical pharmacists contribute to dose adjustment, management of drug interactions, monitoring of cardioprotective therapy, and patient counseling. Their involvement improves medication safety and supports adherence to complex treatment regimens.

12. Special Populations

12.1 Elderly Patients

Elderly patients exhibit reduced cardiac reserve and higher prevalence of comorbidities, increasing susceptibility to cardiotoxicity. Individualized treatment plans and intensified monitoring are essential in this population.

12.2 Pediatric and Young Adult Survivors

Exposure to cardiotoxic chemotherapy at a young age confers lifelong cardiovascular risk. Long- term surveillance is crucial, as late-onset cardiotoxicity may emerge decades after treatment completion.

12.3 Patients with Pre-existing Cardiovascular Disease

Patients with established cardiovascular disease require careful risk stratification and proactive management. Optimization of baseline cardiac function prior to chemotherapy improves tolerance and outcomes.

13. Recent Advances in Cardio-Oncology

13.1 Novel Biomarkers and Imaging Tools

Emerging biomarkers and advanced imaging techniques offer improved sensitivity for early myocardial injury detection. Integration of these tools into clinical practice may enhance preventive strategies.

13.2 Personalized and Precision Medicine Approaches

Advances in pharmacogenomics and risk modeling support individualized cardiotoxicity prediction and prevention. Personalized approaches may optimize therapy selection and monitoring intensity

13.3 Artificial Intelligence in Cardiotoxicity Prediction

Machine learning algorithms show promise in identifying high-risk patients and predicting cardiotoxic events, potentially enabling earlier intervention.

14. Conclusion

Chemotherapy-induced cardiotoxicity has emerged as one of the most significant non-oncologic complications affecting patients with breast cancer and haematological malignancies, particularly as survival rates continue to improve.

Advances in chemotherapy, targeted therapies, and immunotherapies have transformed cancer into a more manageable chronic disease for many patients; however, these gains are increasingly accompanied by short- and long-term cardiovascular consequences that impact quality of life, treatment continuity, and overall survival.

Cardiotoxicity is a multifactorial and dynamic process involving oxidative stress, mitochondrial injury, calcium dysregulation, endothelial dysfunction, and inflammatory pathways. The spectrum ranges from

asymptomatic left ventricular dysfunction to overt heart failure, arrhythmias, hypertension, myocarditis, and ischemic events. Importantly, cardiotoxic effects may be acute, subacute, or delayed sometimes manifesting years after therapy—particularly in survivors of breast cancer and childhood or young-adult haematological cancers. The distinction between reversible (e.g., HER2-targeted therapy–related) and irreversible (e.g., anthracycline-related) damage underscores the need for early detection and timely intervention. Both patient-related factors (age, pre-existing cardiovascular disease, diabetes, hypertension, genetic susceptibility) and treatment-related factors (cumulative dose, combination regimens, radiation exposure, high-dose chemotherapy for transplantation) critically influence risk.

Polypharmacy and pharmacogenomic variability further modify individual vulnerability, making a personalized risk-assessment approach essential.

Early diagnosis through structured surveillance strategies including echocardiography, ECG, cardiac biomarkers (troponins, BNP/NT-proBNP), and advanced imaging—allows identification of subclinical cardiac dysfunction before irreversible damage occurs.

Preventive measures such as dose optimization, use of cardioprotective agents (e.g., dexrazoxane), careful scheduling, and aggressive management of cardiovascular risk factors play a central role in reducing morbidity. Once cardiotoxicity develops, prompt initiation of guideline-directed heart failure therapy, modification of anticancer regimens, and coordinated multidisciplinary care are crucial.

The expanding field of cardio-oncology represents a paradigm shift toward integrating cancer and cardiovascular care. Novel biomarkers, strain imaging, pharmacogenomics, and artificial intelligence–based prediction models hold promise for earlier risk stratification and precision medicine. Within this evolving framework, the clinical pharmacist has a pivotal role in medication review, dose adjustment, interaction screening, patient counselling, adherence support, monitoring of cardiac parameters, and participation in pharmacist-led surveillance models—especially in Pharm D–driven practice settings.

In summary, chemotherapy-induced cardiotoxicity is no longer a secondary concern but a central survivorship issue in breast and haematological cancers. A proactive approach combining risk assessment, early monitoring, preventive strategies, and multidisciplinary management is essential to balance oncologic efficacy with cardiovascular safety. Strengthening cardio-oncology services and pharmacist involvement will be key to improving long-term outcomes and ensuring that cancer cure does not come at the cost of cardiac health.

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