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Review Article

Cardio Oncologist: A Prerequisite for Preventing Cardiac Damage in Cancer Therapy

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Abstract

To strengthen our understanding of cardiac oncology, we studied the fundamentals of oncology, focusing on the cardiovascular system and its effects on cardiotoxicity. The success of basic research and the study of specific diseases make cancer patients one of the fastest-growing subgroups. Interestingly, cardiovascular disorders are the 2nd major cause of illness and death after malignant tumors in cancer patients. A unique approach to addressing the early detection, prevention and treatment of cardiotoxicity in cancer patients has been proposed, for cancer patients as multidisciplinary cardiovascular care. Cancer therapies have been linked to a number of cardiovascular adverse effects, including arrhythmias, hypertension, and ischemic heart disease. This article highlights current practice guidelines for cancer-related therapy's potentially serious cardiotoxicity, as well as the importance, role, and need for a cardio-oncologist.

Keywords: Cardiotoxicity; Cardio-Oncology; Cardiovascular system disease; Cardio-oncologist; Cancer

Introduction

Cardiotoxicity is a common adverse effect of chemotherapy. There have been earlier reports of cardiac failure in children who had been given doxorubicin [1]. Since then, anthracycline-based cytostatic antibiotics have been the most often utilized cardiotoxic chemotherapeutic drugs. A number of other chemotherapy drugs can induce cardiotoxicity, which many doctors are unaware of. Cardiomyopathy, arrhythmias, myocardial infarction, myocarditis, and pericarditis, as well as mild transient blood pressure and ECG abnormalities, can all cause CHF or LVD. The goal of this article is to discuss about the potential for serious cardiotoxicity in current cancer therapies, as well as the following:

A. Cardiotoxicity caused by chemotherapy

B. Cancer and heart-induced cancer therapy

C. Common drug interactions between Cardiovascular Drugs

D. To show the importance of the role and need for a cardio-oncologist

Cardiotoxicity caused by chemotherapy

Chemotherapy's basic principle is to impair the mitotic and metabolic processes of cancer cells. Unfortunately, chemotherapy affects certain normal cells and tissues, resulting in a variety of minor to severe side effects such as bone marrow suppression, nausea, and vomiting, as well as cardiovascular side effects such as hypotension, tachycardia, arrhythmias, and heart failure [1]. According to the National Cancer Institute, Cardiac Toxicity is defined as that affects the heart as cardiotoxicity. Cardiotoxicity is a broad term that should not simply encompass the difference in resting heart parameters. But also the cardiovascular system's recruitable stroke work, coronary blood flow reserve, and dynamic functional evaluation of maximal functional capacity [VO2]. We know that many cancer survivors have decreased exercise capacity, which has a significant impact on their quality of life. Dynamic cardiovascular assessments are important because we know that many cancer survivors have decreased exercise capacity, which has a significant impact on their quality of life. Although various chemotherapeutic drugs can impact cardiotoxicity, as shown in (Table 1), certain kinds of chemotherapy, such as anthracyclines, cause more frequent and common adverse effects [2].

Table 1: Potential cardiotoxicity induced by numerous chemotherapeutic agents.

Class	Examples of Chemotherapeutic Agents	Possible Cardiotoxicity
Anthracyclines and anthraquinones	DOX, mitoxantrone	Congestive heart failure, left ventricular dysfunction, acute myocarditis, and arrhythmia
Antimetabolite agents	Capecitabine, 5-fluorouracil, and cytarabine	Ischemia, pericarditis, congestive heart failure, and cardiogenic shock, vasospasm
Antimicrotubule agents	Paclitaxel, vinca alkaloids	Sinus bradycardia, ventricular tachycardia, atrioventricular block, hypotension, congestive heart failure, and ischemia
Alkylating agents	Cyclophosphamide, ifosfamide	Neurohumoral activation, mild mitral regurgitation
Monoclonal antibody against HER2	Trastuzumab	Arrhythmias, congestive heart failure, angioedema, and left ventricular dysfunction
Antiangiogenic and tyrosine kinase inhibitors	Imatinib, sorafenib, and sunitinib	Hypertension, arrhythmias
Antivascular endothelial growth factor	Bevacizumab	Hypertension, thromboembolism

Patients at high risk of cardiac problems should not be given these medications. Cardiotoxicity is more likely in people with high blood pressure, diabetes, liver illness, or a history of heart disease [3]. Cardiotoxicity is also strongly influenced by the route of administration, the duration of chemotherapy (cumulative Dose), and the dose regimen. Combination of anthracyclines with other potentially cardiotoxic agents, such as paclitaxel or trastuzumab, would significantly enhance the risk of cardiotoxicity, potentially leading to severe heart failure [4-6]. It is even more critical for the health care practitioner to be aware of the cardiac side effects of cancer treatment. Although there is a lack of real consensus on definitions of cardiotoxicity, direct effects on cardiac structures (e.g., fibrosis), cardiac arrhythmias and conduction, systemic, diastolic, hemodynamic, hemostasis, thrombosis, and pulmonary vascular function, as well as a cardiac response to injury and stress, are all factors to consider [4]. During cancer therapy, the tone and specific cardiovascular biomarkers (e.g., troponin I and natriuretic peptides) may reflect subtle alterations of the cardiovascular system that are predictive for the development of HF before drop-in LVEF [5-7].

Cancer and heart-induced cancer therapy

Chemotherapy commonly causes heart failure in cancer survivors, reducing their quality of life and increasing mortality. Classical chemotherapy, immunotherapy, radiation, surgery, and targeted therapies are all part of modern cancer treatment [8]. The most common cardiovascular complication associated with cancer therapy is heart failure. Both traditional and innovative cancer drugs contribute to the development of heart failure [9]. Cardiotoxicity is dose-dependent, but with lower cumulative doses it can also occur [10]. In patients with symptoms of heart failure, it is recommended to begin therapy with cardioprotective drugs. However, evidence-based guidance is limited, and the European cardio-oncology guidelines refer to heart failure recommendations that encourage the use of Angiotensin II Receptor Blockers (ARBs) / Angiotensin Converting Enzyme (ACE) inhibitors and beta-blockers [11-14]. Several studies have been conducted to evaluate whether such treatment, when administered prior to cancer treatment, might prevent the development of heart failure. There is currently limited data to variability in drug selection, trial populations, and cancer entities [15,16]. The most serious complication for cancer patients is still heart failure. Heart failure can develop during therapy or years after it has been completed. Alternative preventive medicines for younger patients (for example, breast cancer patients or children and adolescents with hematological malignancies) have not been thoroughly researched.

At the present, there are no indicators of guidelines. According to existing data, using ARB/ACE inhibitors or beta blockers for

the management of heart failure before starting cancer therapy is associated with a moderate benefit in LVEF in some populations. Of course, patients should be warned about the potential side effects of these medications. The available studies differ with regard to the specific drug, the dosages and the timing (especially with regard to the timing of chemotherapy) and duration of use. Protective effects, which are observed, for example, with a certain beta block, cannot easily be demonstrated within the entire group of active substances (Nebivolol's effect on nitric oxide metabolism). The efficacy of preventive treatments, the timing of drug administration, and monitoring should all be assessed in future research, given the clear correlation between cardiac dysfunction and these patients Furthermore, it remains to be seen whether the potential benefits of the prevention methods found in the studies studied still are evident after cancer treatment and the discontinuation of beta-blockers and ACE/ARB inhibitors, which would answer the question of whether beta-blockers and/or ACE are discontinued. Cardiotoxicity has been enhanced or specifically prevented by ACE inhibitors/ARBs. Surrogate outcomes such as left ventricular ejection fraction evaluated by Echocardiography (ECG) or magnetic resonance tomography (MRI), as well as clinical conditions, quality of life, and impermanence, were contradictory [17].

In canonical heart failure, beta blockers are used to decrease sympathetic activity, reduce heart rate, and improve excitation-contraction coupling. ACE/ARB inhibitors are medications that are used to reduce cardiac remodeling and control blood pressure. Finally, ACE inhibitors and beta-blockers ensure that LVEF is kept as low as possible [18]. These preventative treatments can be initiated for patients who are at risk of receiving standard high-dose chemotherapy, especially those with risk factors. Pre-existing cardiovascular risk factors for chemotherapy-related heart failure, not only in terms of LVEF preservation, but also of quality of life and survival. It is also the immediate focus of cardio-oncology research, which is becoming increasingly important as new, more active chemotherapies become available.

Cardiotoxicity associated with radiation therapy

Radiation therapy is used to treat various types of cancer. Chest radiation can damage the pericardium, myocardium, valves, and coronary arteries, with the pericardium being the most commonly affected. Radiotherapy can cause silent vascular damage; roughly 50% of asymptomatic individuals acquire new myocardial perfusion defects. Most of the patients present with angina, dyspnea, or heart failure [19]. Despite the fact that sudden death has been reported [20]. Unexpected mortality in radiation therapy patients is thought to be caused by diffuse intimal hyperplasia of coronary arteries or left main stenosis [21]. It also causes pericardial fibrous thickening. Pericardial effusion is an early manifestation, while pericardial effusion is a late manifestation that generally arises after 18 months. Radiation treatment can potentially cause myocardial fibrosis. Fibrosis is characterized by significant changes in collagen synthesis [22]. Because radiation promotes fibrous thickening of the heart valves, valvular heart disease is also common following radiation [21,23].

Cardiovascular toxicity monitoring

Anticancer drugs related for monitoring cardiotoxic effects such as arrhythmias, ischemic cardiac events, and pericardial disease should be specifically planned and adapted to each therapeutic protocol under which anticancer agents are prescribed. Cardiac tests such as electrocardiography (ECG), myocardial perfusion a rest and stress imaging, and troponin levels to monitor ischemic cardiac complications. This ECG is crucial in detailed evaluation of valvular heart disease, evaluating pericardial disease and the left ventricular systolic and diastolic function. Doppler echocardiography can also be used to assess hemodynamic status, including involvement of pulmonary hypertension [24].

Drug interactions between chemotherapy and cardiovascular drugs in cancer patients with pre-existing cardiovascular disease

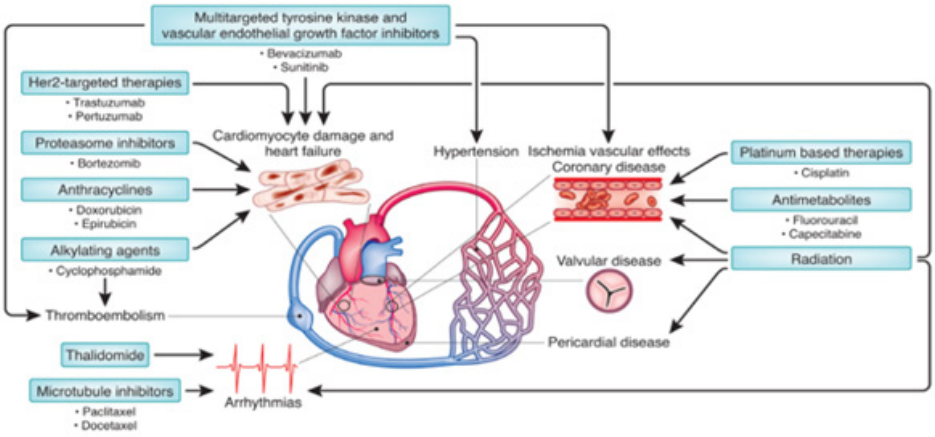

Figure 1: An overview of the cardiovascular side effects of chemotherapy and radiation [27].

As the field of cardio oncology has advanced, the emphasis of treatment has switched from reactive to proactive therapy. Monitoring and short interruptions in cancer treatment are critical components of contemporary treatment paradigms.

Heart medications such as beta-blockers, Angiotensin-Converting Enzyme Inhibitors (ACEI) or Angiotensin Receptor Blockers (ARBs), and statins are commonly used in combination with various chemotherapy drugs [25,26]. Because most chemotherapy treatments have a limited therapeutic window, factors that contribute to drug-drug interactions can improve or reduce chemotherapy efficacy or predispose patients to serious unfavorable side effects. These drug-drug interactions are very common in the cancer patients; one of the study showed that 16% patients had at least one serious interaction with drugs that could cause adverse side effects in patients receiving oral anticancer drugs. In the context of cancer treatment, healthcare practitioners should be mindful of possible drug-drug interactions and reduce complications when managing health of cardiovascular patients. In the following discussion of drug-drug interactions including common chemotherapy and cardiac drugs, Pharmacokinetics (PK) and Pharmacodynamic Interactions (PD), antithrombotic, and QT interval prolongation are all areas of concern (Figure 1).

Interactions Between Pharmacokinetics and Pharmacodynamics Mechanisms

A pharmacodynamic and pharmacokinetic mechanism causes a drug-drug interaction. A pharmacodynamic interaction occurs when two drugs with identical molecular targets interact in a way that is additive or synergistic, resulting in an exaggerated clinical reaction or toxicity. The P-glycoprotein efflux pump and CYP450 enzymes are two of the most significant pharmacokinetic interactions in oncology [28,29]. The gastrointestinal tract metabolism is controlled by CYP enzymes [29]. Dose reduction or use of a different statin (different metabolic pathways). Atorvastatin, Simvastatin, and Lovastatin are all metabolized by CYP3A4. During Idelalisib therapy, we should consider other statins that do not undergo CYP3A4 metabolism (e.g., pravastatin, fluvastatin, and rosuvastatin) (as shown in table 2).

A variety of chemotherapeutic and cardiac drugs contain CYP450 inhibitors and substrates. They may be involved in dual drug interactions since they are both substrates and antagonists. P-glycoprotein (P-gp), an ATP binding cassette transporter family protein, is expressed in the intestinal epithelium and functions as an efflux pump, successfully exporting drugs from the cell cytoplasm to the lumen (gut); P-gp substrates include vinblastine, vincristine, doxorubicin and paclitaxel [29]. The concomitant administration of calcium channel blockers, beta blockers, and other medications causes polymorphic ventricular tachycardia. These medications may produce abnormally long QT intervals (Table 2).

Table 2: Drug-Drug interactions of common cardiac drugs and chemotherapeutic agents.

Cardiac Drug(s)	Enzyme/ Action	Chemotherapy Drug†	Effect of Drug-Drug Interaction	Suggested Oncologist Management	Suggested Cardiologist Management
All betablockers	Additive clinical effect	Ceritinib	Additive bradycardia	Avoid using the combination of ceritinib with betablockers. If concomitant use is necessary and symptomatic bradycardia occurs, hold ceritinib, adjust or discontinue the beta-blocker, and upon recovery resume ceritinib at a reduced dose with frequent monitoring of heart rate.‡	
Angiotensin Receptor Blocker(ARBs) Losartan	CYP3A4 inhibition (strong)	Idelalisib	↑ losartan concentration	Notify cardiologist/ prescriber to switch to alternative therapy.	Avoid co-administration. Consider alternative agent during Idelalisib therapy that does not undergo CYP3A4 metabolism (i.e., irbesartan, valsartan)
Calcium Channel Blockers Verapamil; Diltiazem	Additive clinical effect	Ceritinib	Additive bradycardia	Avoid using the combination of ceritinib with non-dihydropyridine calcium channel blockers. If concomitant use is necessary and symptomatic bradycardia occurs, hold ceritinib, adjust or discontinue the calcium channel blocker, and upon recovery resume ceritinib at a reduced dose with frequent monitoring of heart rate.‡	
Diltiazem; verapamil	CYP3A4 inhibition (moderate)	Bosutinib	↑ chemotherapy drug concentration	Notify cardiologist/ prescriber to switch to alternative therapy.	Avoid co-administration.‡ Consider alternative agent during bosutinib therapy that does not inhibit CYP3A4.
Amlodipine	CYP3A4 inhibition (strong)	Idelalisib	↑ amlodipine concentration	Notify cardiologist/ prescriber to switch to alternative therapy.	Avoid co-administration. Consider alternative agent during Idelalisib therapy. If concomitant use is necessary, closely monitor for adverse effects due to amlodipine (i.e., hypotension, peripheral edema)
Statins Atorvastatin Simvastatin Lovastatin	CYP3A4 inhibition (strong)	Idelalisib	↑ statin exposure; increased risk of myopathy and rhabdomyolysis	Notify cardiologist/ prescriber to switch to alternative statin therapy.	Avoid co-administration. Consider alternative statin that does not undergo CYP3A4 metabolism (i.e., pravastatin, fluvastatin, and rosuvastatin) during Idelalisib therapy.

Cardiac Glycoside Digoxin	Additive clinical effect	Ceritinib	Additive bradycardia	Avoid using the combination of ceritinib with digoxin. If concomitant use is necessary and symptomatic bradycardia occurs, hold ceritinib, adjust or discontinue digoxin, and upon recovery resume ceritinib at a reduced dose with frequent monitoring of heart rate.‡
	P-gp inhibition	Vemurafenib	↑ digoxin drug concentration	Avoid co-administration if possible. If concomitant use cannot be avoided, consider digoxin dose reduction and monitor levels and signs/symptoms of digoxin toxicity closely.
Anti-Arrhythmic Amiodarone Dofetilide Dronedarone Flecainide Sotalol	Additive clinical effect	High risk QTc prolongers Arsenic Trioxide*† Nilotinib† Toremifene Vandetanib*†	Additive QTc prolongation	Recommend ECG and electrolyte monitoring. Frequency to be determined by patient-specific factors and QT prolonging drug risk. Avoid combination of high-risk QT prolonging chemotherapy and cardiac drugs (i.e., arsenic and Dofetilide).
† Color denotes severity of interaction as follows:				
• Red. Major interaction; Black Box warning and/or strong clinical effects; avoid combination.				
* Known incidence of TdP.				
† Package insert includes ECG monitoring parameters.				

Cardio-Oncologist - Importance, Role and Need

The cardio-oncology association's ultimate aim is to diagnose chemotherapy cardiotoxicity with a broad understanding, not to discourage or avoid oncological care, but to begin medical therapy or lifestyle modifications in the hopes of improving survival outcomes. In modern civilization, cancer and cardiovascular diseases are the leading causes of impermanence and death. Cured cancer patients aged 65 and over will increase from approximately 62% to 73% by 2040, which in turn will improve comorbidity [30]. The burden of cancer-related cardiovascular disease and cancer therapy was revealed in cancer patients with increasing age and survivors [31]. Early cardiotoxicity is observed in up to 48% of patients, and late cardiotoxicity can be found in 30% of patients 13 years after cancer treatment depending on the cancer treatment modalities [19,12,25]. Cardio-oncology focuses to recognize the associated cardiovascular adverse effects of cancer treatment and ensure optimal interdisciplinary chemotherapy. Research efforts have produced a deep understanding of the underlying clinical relevance and pathogenesis, but standard guidelines and structural requirements for the treatment of cardiovascular malignancies remain limited [12,25,32].

The diagnosis of cardiac problems associated with cancer treatment is complex. Population heterogeneity makes it difficult to compare groups and between groups. It is often impossible to conduct large enough population studies, and the number of new drugs used to treat other diseases makes it difficult to evaluate large populations. Identify patients related to cancer treatments, who are at higher risk of cardiovascular problems or who have symptoms on one side. Post-treatment effects are an important aspect of a growing field known as cardio-oncology. Oncologists, in collaboration with cardiologists, can provide the assistance needed by those who are primarily clinicians treating cancer patients in order to improve therapy. The aim should be to augment meaningful life in every way imaginable. Excessive concern about potentially reversible heart issues can hinder the delivery of highly successful cancer treatments, while underestimating cardiac risk in a cancer-free patient can result in lifelong heart problems, a careful balance requires careful consideration of the needs of these diverse patients. The best chance of long-term disease-free survival for these individuals is to be aware of the cardiac effects of anticancer drugs, in consistent with knowledge of the normal course of malignancy and the risk of a tumour reaction [32].

Some cardiovascular mechanisms have become clearer as a result of research into the negative effects of newly emerging cancer therapies. The erbB2/ HER2 / neuregulin signaling pathway, which has been the focus of many cancer treatments, is thought to play a role in cardiovascular homeostasis, and research is underway to evaluate stimulation of this pathway may benefit patients with heart failure. Intense studies and ongoing clinical trials in oncology are the subject of signal inhibitors, chemotherapeutic agents, and combinations of these [33]. The cardiovascular adverse effects of these drugs should be expected based on their direct effect on signal transduction or the potential for additional non-targeted inhibitory effects [34]. Specific topics and priorities highlight the current state of the field as presented in each conference and to the extent possible, strategies to move the field forward in a targeted manner [35]. Since clinical and basic research data inform the analysis of our clinical practice in so many ways that need to be developed, the aim is to help identify the key knowledge gaps that need to be filled in order to understanding and improved clinical care for our patients.

They highlighted the importance of a cardio-oncology programme in the prevention, early detection and reduction of the impact of cancer treatment on the cardiovascular system in hospital and community settings. Given the rising number of FDA (Food and Drug Administration) approved anti-cancer agents with possible cardiotoxic effects, better screening before beginning anti-cancer therapy is crucial to avoiding cardiotoxicity in cancer and heart disease with similar risk factors. Clinicians are invited to identify what preventive measures should be used to reduce

the risk of cardiotoxicity in patients at risk of developing cardiac dysfunction prior to initiation of therapy, during treatment with potentially cardiotoxic anti-cancer agents, and to evaluate preferred approaches to monitoring and follow-up after treatment. Cardio-oncology is also considered consistent with cancer therapy for the treatment of cardiovascular toxicity; it is important to note that there are many common risk factors and pathological mechanisms between cancer and cardiac disease at the cellular and molecular levels that can be easily detected by a clinical pharmacist [36]. Cardiac toxicities due to cancer treatment include heart failure, cardiac ischemia, arrhythmias, pericarditis, valvular disease, and fibrosis of the pericardium and myocardium [37].

Although cardio-oncology departments have been established in parts of Europe and the United States, it is still a relatively new concept in the United Kingdom and many other countries, but a clear clinical need is leading several hospitals to develop standard cardio-oncology services such as Bart's Heart Center [38], St Bartholomew's Hospital in London, and University College London Hospital [39], and this issue is also reflected in several recent Cardio-Oncology guidelines. Cancer patients may present with a variety of cardiovascular problems that are not all directly related to anticancer therapy (drugs or radiotherapy) [25,40]. Optimal individual management requires a close collaboration between cardiology and oncology specialists.

Conclusion

Cardiac toxicity is a problem that affects cancer patients' quality of life and well-being. To develop preventative measures based on the early identification and preventative measures of cardiotoxicity, a thorough evaluation of these patients' needs is needed. To standardize the treatment process, cardio-oncology multidisciplinary teams must combine their abilities and skills. Also, a clinical pharmacist should be integrated with the multidisciplinary team responsible for the treatment of cancer patients to evaluate the potential drug interactions. This recognition has aided in the stimulation of collaboration among oncologists, cardiologists, and researchers, and integrated discipline of cardio-oncology can have the results in many medical centers. This collaboration aims perception into how cancer treatments lead to long-term effects on cancer patients and cardiovascular homeostasis. The most recent perspectives on cardiotoxicity with different classes of chemotherapeutic agents and drug-drug interactions with cardiovascular drugs in cancer patients with pre-existing cardiovascular diseases were discussed in this review. We also discussed the importance, role, and necessity of a cardio-oncologist.

Conflict of Interest: Authors declare that they have no conflict of interests

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