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Investigation of some chemotherapy drugs induce cardiotoxicity

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ABSTRACT: The risk of long-term cardiovascular problems resulting from cancer treatment is rising due to the growing population of cancer patients. Cancer therapy-induced cardiotoxicity (CTIC) is a partially elucidated consequence of diverse chemotherapeutic drugs, targeted anti-cancer treatments, and radiation treatment. It is usually identified clinically by a decrease in left ventricular ejection fraction, evaluated by echocardiography. Nonetheless, the emergence of cardiac functional decline signifies irreparable heart injury, underscoring the need for the development of diagnostics capable of identifying CTIC before the commencement of functional deterioration. Growing evidence indicates that abnormal changes in heart metabolism significantly contribute to the onset of CTIC. The treatment progress has significantly enhanced the recovery rate of cancer patients. This better longevity is concomitant with increased risks for cardiovascular complications. Chemotherapy-induced cardiotoxicity is a perilous outcome that limits the therapeutic use of various chemotherapy agents. This review analyses the prevalence of heart disease is caused by immunotherapeutic medicines and chemotherapy. The preventive characteristics of antioxidants and future possible concerns about cardiotoxicities caused by treatment are the primary topics of discussion in this study.

Keywords: Cardiotoxicity, Chemotherapy, Heart failure, Cardio protection, CTIC

1. INTRODUCTION

The progression of medicine knowledge is linked to a paradigm change in novel anticancer medicines, resulting in a substantial enhancement of life expectancy in patients [1]. Despite significant advancements in cancer chemotherapy, the severe side effects linked to the treatment remain a substantial concern [2]. The cytotoxic properties that result from medicine affect each primary organ, and signs and symptoms are associated with developing other medical conditions. Cardiotoxicity is the primary adverse effect linked to chemotherapy treatment; therefore, the enhancement of lifespan from this type of therapy may be compromised by a heightened death risk from cardiac problems. Cardiotoxicity may appear at any phase of medications, presenting as modest cardiac dysfunction to irreparable cardiac failure and fatality [3].

Cardiotoxicity is a very concerning consequence of contemporary cancer treatment. Cardiotoxicity may restrict ongoing cancer therapy and may manifest years after treatment concludes in survivors. Cancer specialists and cardiac

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surgeons treating patients with cancer must understand the quick detection of damaged myocardium, avoiding heart failure, techniques for quick restoration of heart function after injury, and surveillance for later effects of cancer treatment [4].

A specialization in cardio-oncology has emerged to enhance focus on these areas. Different Heart diseases may present as cardiac arrhythmia, myocardial infarction (MI), and cardiac failure. The World Health Organization's standards categorize cardiac toxicities into acute, subacute, and chronic based on their onset [5]. The cardiotoxicity induced by anticancer treatment is variable. The interval between treatment and identification, together with the associated risk factors for cardiovascular disease, may lead to either lasting or reversible damage to the myocardium, depending on the kind and dose of the medicine [6].

Chemotherapy acts by impairing cancer cells' physiological and proliferative activities, often causing unintended harm to normal cells and tissues. This may result in a range of adverse effects, including moderate to serious gastrointestinal problems, bone marrow suppression, and cardiovascular problems such as heart disease, hypertension, and others [7].

Cancer medicines containing structural-specific treatments, toxic therapy, and mediastinal radiation treatment are linked to myocyte damage and transmission, dysfunction of the side ventricle, heart failure, and additional cardiovascular problems [8].

A wide variety of biochemical investigations into the many processes associated with Heat damage. Drugs used for chemotherapy provoke cardiotoxicity via raising the synthesis of nitrogen species and reactive oxygen. Although peroxisomes, along with other organelles within cells, are crucial controllers of redox equilibrium, mitochondria are the principal focus of cardiotoxicity generated by chemotherapy [7].

Anthracyclines (ANT), such as doxorubicin, alkylating agents like cyclophosphamide, and taxanes like docetaxel, are predominant chemotherapeutic agents associated with significant cardiac complications [9].

This review aims to provide insight into certain commonly used cancer therapeutics and their associations with cardiotoxicity.

2. CYTOTOXIC DRUGS CAUSING CARDIO TOXICITY

2.1 CYCLOPHOSPHAMIDE-INDUCED CARDIOTOXICITY

Cyclophosphamide is an antineoplastic agent having tumor-inhibiting characteristics often used in humans treating various malignancies. Numerous publications have demonstrated that, besides its tumor-selective features, cyclophosphamide exhibits a range of potentially dangerous adverse effects, several severe of which are cardiotoxicity, as shown in Figure 1 [10-12].

Cyclophosphamide undergoes metabolism by the Hepatic cytochrome P450 enzyme, resulting in the formation of 4-hydroxycyclophosphamide [13]. The antineoplastic efficacy of cyclophosphamide is describing as phosphoramide mustard, its principal medicinal metabolism, which possesses DNA alkylation action. In contrast, acrolein, a metabolite of cyclophosphamide, impairs the antioxidant system [10- 14].

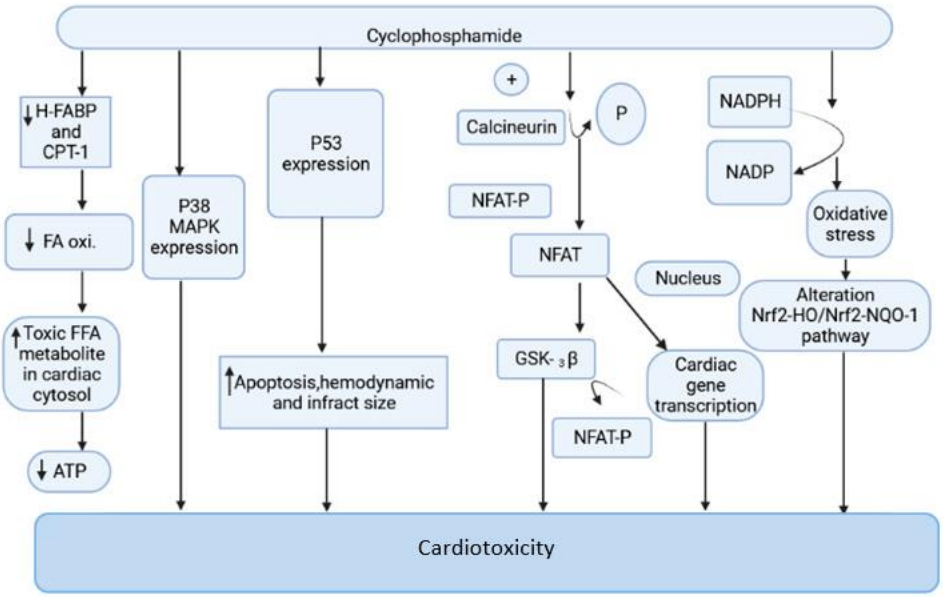

FIGURE 1. - The process of heart damage induced by cyclophosphamide [15]

2.2 DOXORUBICIN-INDUCED CARDIOTOXICITY

Doxorubicin (DOX) is an anthracycline antibiotic initially obtained from the bacterium Streptomyces peucetius in the beginning of the 1960s and initially employed as a cytotoxic agent in 1969. It is a quite efficacious therapeutic drug for different tumors due to several side effects, with cardiac reduction being the biggest danger [16].

Patients with advanced cancer who received several doses of doxorubicin for over a month had significant cardiac toxicity symptoms, with an incidence exceeding 30%. The extensive array of symptoms included ventricular failure, a reduction in the QRS section, myocardial dilation, tachycardia, and hypotension. The individuals exhibited no response to inotropic drugs or circulatory support via mechanical devices. Multiple biomarker levels, such as creatine phosphokinase, serum glutamic-oxaloacetic transaminase, and lactate dehydrogenase, were elevated [17-19].

2.3 TRASTUZUMAB-INDUCED CARDIOTOXICITY

This monoclonal antibody is used for treating breast cancer patients with high levels of human epidermal growth factor receptor 2 (HER2, sometimes referred to as ErbB-21). While trastuzumab therapy has shown to reduce mortality and morbidity in breast tumor individuals, substantial heart problems need monitoring. HER2 is a crucial target for breast cancer and, hence, a principal focus for trastuzumab. Nonetheless, many mutant mouse models have shown that ErbB-2 genes are crucial for prenatal cardiomyocyte activity and growth [20].

The probability of experiencing trastuzumab-induced cardiotoxicity increases in patients receiving concurrent the drug's therapy [21]. Trastuzumab, by inhibiting ErbB2 signaling, reportedly enhances the capacity of anthracyclines to trigger the degradation of sarcomeric proteins. Figure 2 illustrates the etiology and molecular mechanisms associated with trastuzumab-induced cardiotoxicity [22].

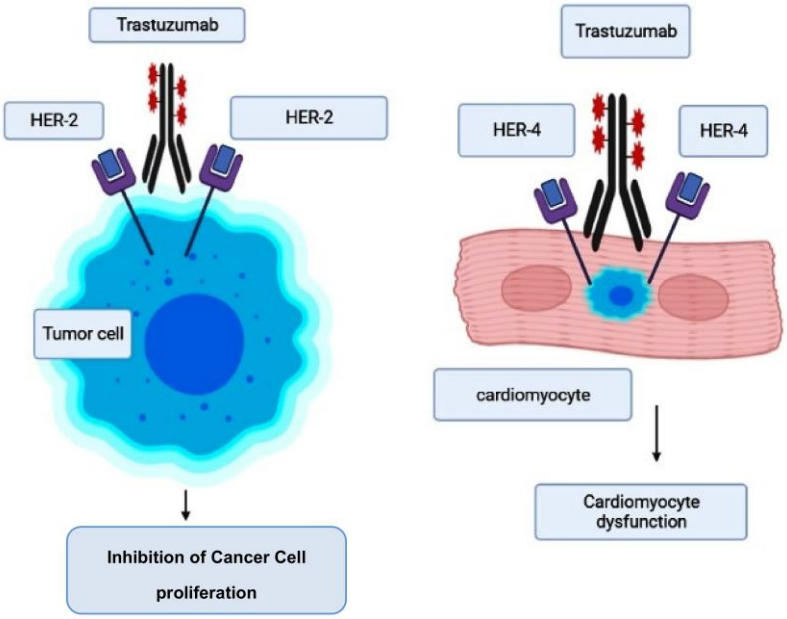

FIGURE 2. - Mode of action of trastuzumab and its cardiotoxicity induction [22]

2.4 FLUOROURACIL-INDUCED CARDIOTOXICITY

5-fluorouracil (5-FU) is a pyrimidine analogue used as a chemotherapeutic agent for several malignancies [23]. Figure 3 depicts the likely mechanisms behind 5-FU-induced cardiotoxicity. The condition usually occurs with infusions; however, it may sometimes present many hours post-administration of 5-FU. Severe or life-threatening cardiotoxicity is rare, happening at a rate of around 0.55 percent [24, 25]. The precise mechanisms behind 5-FU-induced cardiac toxicity remain unidentified, while coronary artery spasm is proposed as a potential possibility. Consequently, it is advised that a heightened awareness of potential cardiac toxicity be retained while administering 5-FU to cancer patients [25-27].

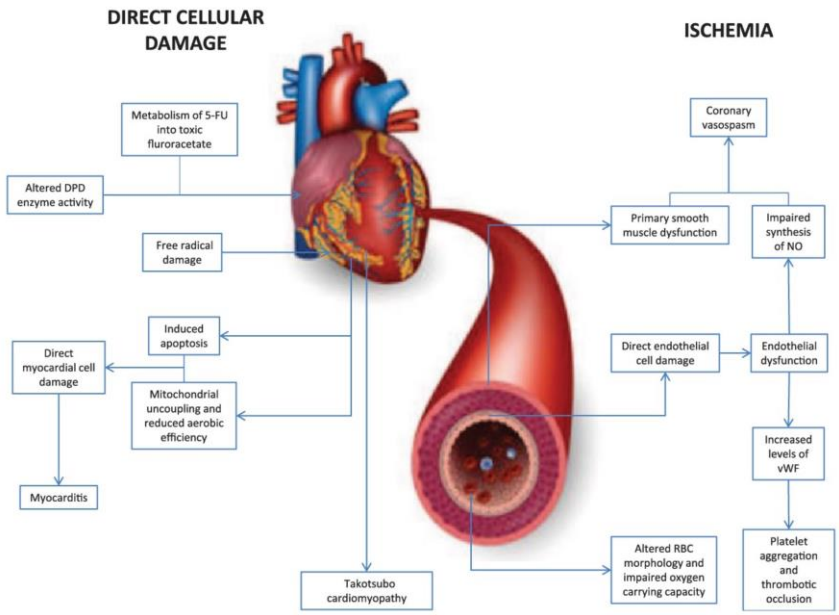

FIGURE 3.- A diagram representation of the two primary mechanisms of 5-fluorouracil-induced heart disease [24]

2.5 CISPLATIN-INDUCED CARDIOTOXICITY

Cisplatin, or cis-diamminedichloroplatinum (CDDP), is an exceptionally potent chemotherapeutic agent. In conditions such as ovarian, cervical, and testicular cancer, it is used either as a monotherapy or in combination regimens. Nevertheless, owing to detrimental consequences, such as nephrotoxicity, hepatotoxicity, and gastrointestinal problems, the therapeutic use of cisplatin is limited [28]. Notwithstanding these adverse effects, many survivors of cisplatin therapy may have acute or chronic cardiovascular problems that may detrimentally affect their quality of life. CDDP-induced cardiomyopathy is associated with heart and supraventricular arrhythmias, intermittent sinus arrest, electrocardiographic abnormalities, infrequent complete atrioventricular block, and congestive heart failure. Oxidative stress is regarded as a primary contributor to cardiac injury associated with cisplatin-based treatment. Cisplatin-based treatment exhibited the concentrations of a few antioxidants in individuals. Tumor growth may also produce reactive oxygen species (ROS). These variables together result in congestive heart failure and cardiac arrest [28-30] .

2.6 IMMUNOTHERAPY-INDUCED CARDIOTOXICITY

At first, the body's immune system inhibits tumour proliferation throughout cancer development. Despite this, tumors have the ability to circumvent every pathway that are responsible for facilitating immunologic protective responses. The pathways consist of immunology regulatory mechanisms, including cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), regulated cell division ligand 1 (PD-L1), and regulated cell death protein 1 (PD-1), which serve as conventional impediments that diminish T cell efficacy against malignancies. As a consequence of this, a number of studies were carried out to investigate whether or not stimulating an immune system response to tumors in individuals with cancer might potentially improve the effectiveness of cancer therapy. Since that time, immunotherapy has come into existence. Nevertheless, the benefit of an activated immune system comes at an expense additional, as both treatments have been linked to a wide range of cardiovascular complications. These complications include hypotension, arrhythmia, left ventricular dysfunction, and myocarditis. Clinical manifestations of these complications range from asymptomatic increases in biomarkers of cardiovascular disease to heart failure and cardiogenic shock [31].

2.7 ANTHRACYCLINES

Anthracyclines are often used antineoplastic agents, efficient against malignancies including leukaemia, lymphoma, and many solid tumours. The prevalence of congestive heart failure is less than 5% with cumulative anthracycline exposure below 250 mg/m²; it approaches 10% for doses ranging from 250 mg/m² to 600 mg/m² and surpasses 30% for doses over 600 mg/m² among paediatric cancer survivors. Approximately 60% of all paediatric cancer survivors have been exposed to anthracycline chemotherapy, chest radiation, or a combination of both [32].

Initial toxicity may manifest within a few weeks or months. It often relies on dose-dependent effects. Ventricular issues and heart failure are often included among the enumerated hazards. The prevalence may range from 1% to 18%. A recent extensive study including 2,625 individuals undergoing anthracycline therapy revealed a 9% incidence of cardiac injury. This kind of cardiotoxicity is characterized by a reduction in left ventricular ejection fraction (LVEF)

exceeding 10% and dropping below 50%. It is noteworthy that 98% of patients were detected during the first year after the administration of medication. Furthermore, late toxicity may manifest years after the original injury and is consistently dose-dependent. The principal features of the ultimate consequences are left cardiac systolic failure, diastolic failure, diminished cardiac contractility, ventricular dysfunction, and heart failure. Other features encompass cardiac failure [33].

In a retrospective cohort study of 10,724 childhood cancer survivors, those who survived for five years exhibited an elevated risk of cardiotoxicity and associated death, attributable to anthracycline chemotherapy and radiation, with a dose-dependent relationship [34].

Chemotherapeutic agents linked to cardiotoxic side effects include cyclophosphamide, ifosfamide, cytarabine, cisplatin, paclitaxel, fluorouracil, and amsacrine. While guidelines exist for evaluating heart disease linked to anthracyclines and trastuzumab, no specific procedures are established to follow patients receiving treatment devoid of anthracyclines. Anthracyclines ,including cyclophosphamide, cytarabine, cisplatin, and tyrosine kinase inhibitors [34].

The potential mechanisms of cardiotoxicity associated with several cardiotoxic pharmaceuticals. Nonetheless, the most extensively researched chemotherapy is the cardiotoxicity generated by anthracyclines as shown in Figure 4.

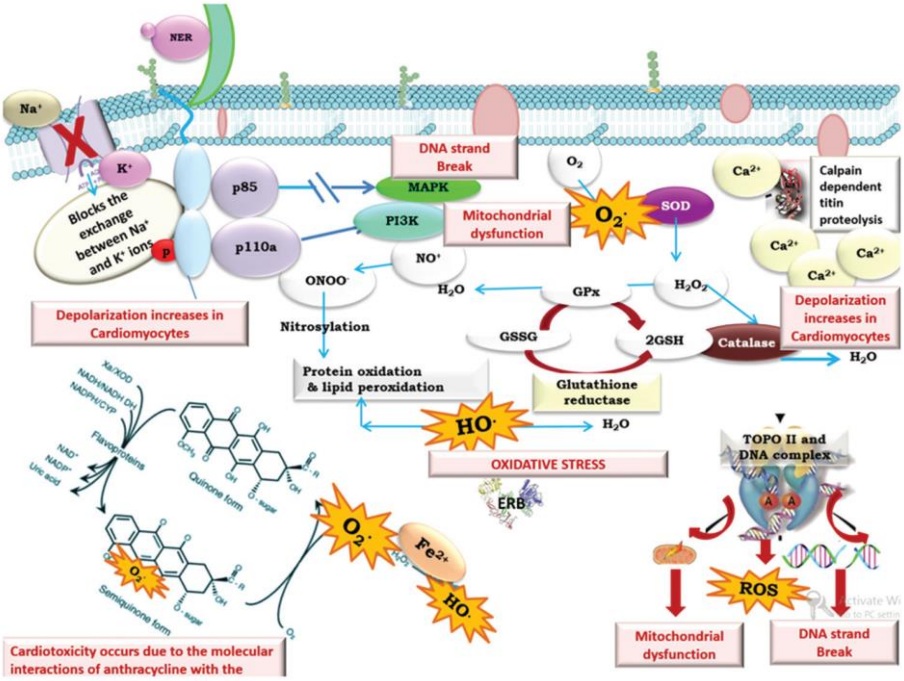

FIGURE 4. - Depiction of the potential mechanisms by which anthracyclines may induce cardiotoxicity. Na+: Sodium ion; GSSG: Oxidised glutathione. K+: Potassium ion, O2: Oxygen free radical, Ca2+: Calcium ion, HO: Hydroxy free radical, P: Phosphate. Reactive oxygen species (ROS): MAPK: Mitogen-Activated Protein Kinase. TOPO II: Topoisomerase II, SOD: Superoxide Dismutase, ERB: Oestrogen Receptor Beta, GSH: Reduced glutathione; ONOO: Peroxynitrite [35]

2.8 RADIATION THERAPY

Cardiotoxicity refers to the effect that radiation therapy has on the cardiovascular system. Damage like this may occur even when the heart is only exposed to a little radiation [35]. Radiotherapy damages tumor cell DNA by employing radiation with high energies or vibrations like X-rays, gamma rays, or particles with charge. This harm prevents cell reproduction and repair, causing death. Cells in the body additionally get harmed, although they replace DNA better than tumor cells. However, the occurrence of heart injury is more likely to occur in patients who are undergoing radiation therapy in conjunction with the administration of chemotherapy medications. Radiation has a key role in the production of heart disease, especially when chest-directed radiation has been administered. Persons who have undergone radiation therapy at earlier ages are more likely to experience cardiotoxicity [26, 27]. This is especially true for persons who have been diagnosed with pediatric malignancies, Hodgkin's lymphoma, early-stage breast cancer, lung cancer, and oesophageal cancer. Radiation-induced cardiotoxicity is often one that develops gradually and is complex. When the dosage is more than 30–35 Gy, the dose per fragment is greater than 2 Gy, the patient is younger, the time of exposure is longer, and when coupled with chemotherapies, the risk of cardiotoxicity is often present [36].

The spectrum of radiation-induced cardiotoxicity encompasses [32] [36]:

1. Short-term and chronic pericardial effusion are both conditions that may be either symptomatic or asymptomatic and commonly manifest between six and twelve months after cancer treatment with radiation.

2. Fibrosis of the conductivity mechanism, myocarditis, congestive heart failure, and valve stenosis are all conditions that may affect the function of the heart.

3. Arteritis that manifests itself in the endothelium of the heart arteries ten to fifteen years after radiation has been administered.

4. Some of the factors that might increase the likelihood of experiencing post-radiation heart disease consist of the amount of the cardiovascular system that is in contact with electromagnetic radiation, the total and divided amounts that are provided, the length of time that the patient is followed up with, and the age at the therapy begins [32].

The medical management of illnesses and defects of the esophagus and stomach, amongst other people, may be accomplished via the application of radiation therapy. After receiving radiation treatment for malignant tumors in the chest, a very common way to diagnose radiation therapy-induced heart disease was to receive chemotherapy [34]. Women all over the world are affected by breast cancer, which is one of the most common forms of cancer within the female population. Because it has been shown to reduce the number of deaths that occur as a result of breast cancer, radiotherapy is presently considered to be a standard component of the several available therapies. Continuously cardiotoxicity in breast cancer patients who are getting radiation therapy is related with a greater possibility of cardiac toxicity that is between 1.2 and 3.5 times higher. This is because of greater radiation exposure to the heart that occurs throughout the course of therapy. The mechanism through which radiation treatment induces cardiovascular disease remains incompletely elucidated; nonetheless, it is believed to initiate irritation, resulting in dysfunction of endothelial cells, microvascular changes, and the accelerated progression of atherosclerosis in the artery walls. The formulation of suitable dose limitations for heart function and the advancement of methods to mitigate the possible cardiotoxic effects associated with electromagnetic radiation are the focus of many studies [35].

2.9 RISK FACTORS AND PREVALENCE

Radiation therapy, chemotherapy, and surgical procedures are the three main components of cancer treatment, both Radiation and chemotherapy are significantly contribute to heart damage [32]; several variables impact the cardiotoxicity generated by cancer treatment as shown in Figure 5.

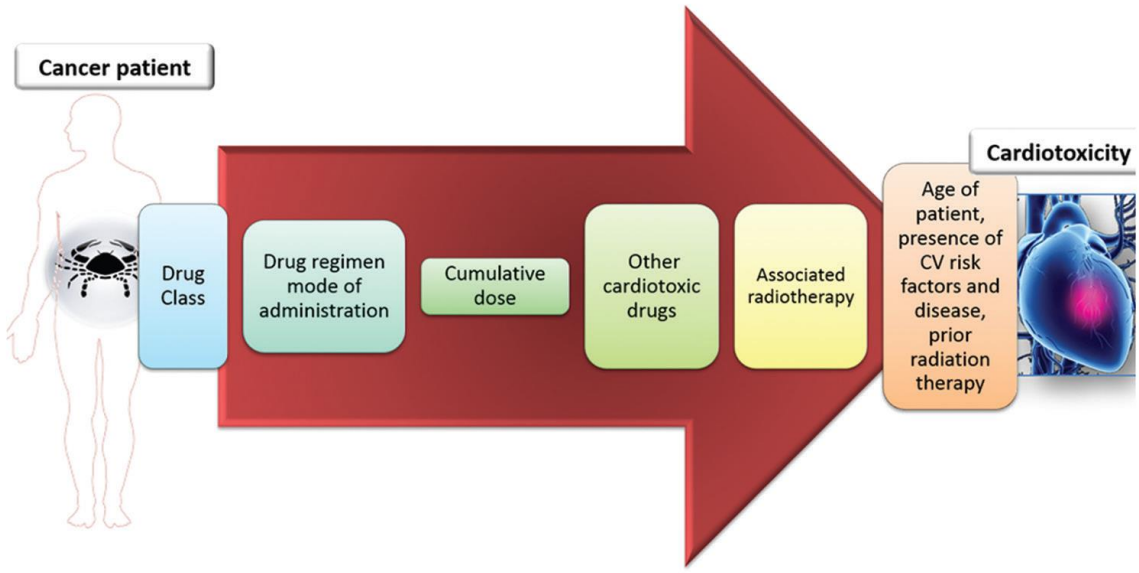

FIGURE 5. - Risk factors linked to the differential course of chemotherapy-induced cardiotoxicity [32]

2.10 ASSESSMENT OF CARDIOTOXICITY

Patients Cancer Therapy with possible cardiotoxicity require vigilant monitoring for acute toxic effects during treatment and the emergence of acute cardiac consequences post-therapy. The objective during therapy is to detect the first indicators of cardiotoxicity to adjust a patient's treatment regimen, therefore reducing the risk of further heart disease progression. These adjustments must be weighed against the dangers of diminished antitumor efficacy that may arise from medication alteration. Patients post-therapy may require continuous surveillance for delayed cardiotoxic effects, particularly if they have been given high dosages of anthracyclines and/or mediastinal radiation [35].

2.11 CANCER IMMUNOTHERAPY

Cancer immunotherapy is an emerging therapeutic modality that relies on a comprehensive knowledge of antitumor immune response mechanisms, the discovery of novel anticancer agents (such as peptides and vaccines), and

the advancement of breakthrough gene transfer technologies. Contemporary cancer immunotherapy using inhibitory mechanisms on immune checkpoint receptors has shown significant efficacy in several malignancies and has yielded encouraging clinical results across diverse cancer types over the last decade. This transformative method has ushered anticancer therapy into a new epoch [37]. It uses antibodies to find and kill tumour cells, thereby revolutionising medicine. Conventional treatments attack tumour cells in person, but therapy boosts the ability of the immune system to fight disease. When it comes for treating a variety of solid tumors, adoptive T cell transfer (ACT) is a new and promising method. Through the use of a patient's T lymphocytes, ACT can target cancerous cells specifically. In a patient's microenvironment, tumor-infiltrating lymphocytes (TILs) are mechanically collected and genetically altered. Systemic interleukin-2 helps TILs survive and multiply. ACT's efficacy as a treatment for metastatic melanoma has laid the groundwork for many modifications and enhancements to target other malignancies (29). Adoptive cell transfer using autologous tumor-infiltrating lymphocytes may decrease metastatic melanoma tumours in 50% of patients. IL-2 is an innate immune cytokine. It has several immunological functions and has been used to treat cancer, causing tumour regression. IL-2 directly affects T cell subset formation in response to antigens, boosting the immune system's defences (30). A recent clinical trial found that lymphodepletion conditioning chemotherapy, autologous TIL infusion, and high-dose IL-2 (24). Similar to B-ALL, chimeric antigen receptor (CAR)-T treatment has showed promise. Like ACT, CAR-T genetically modifies normal T-cells to express a chimeric antigen receptor. The receptor's exterior binding domain lets it recognise and bind tumour antigens. CAR-T's internal activation domain activates the T-cell when it connects to its target [37, 38].

Nevertheless, the therapeutic benefits are diminished by cardiovascular risks that are equivalent to those of the intervention. This is especially true for immunotherapies, since activated T cell responses may not be selective for cancer cells. As a consequence, they might have an effect on healthy tissue, which can lead to immune-related adverse events (IRAEs) that are prevalent, such as colitis, thyroid disorders, liver disease, and pneumonia [38], as figure 6.

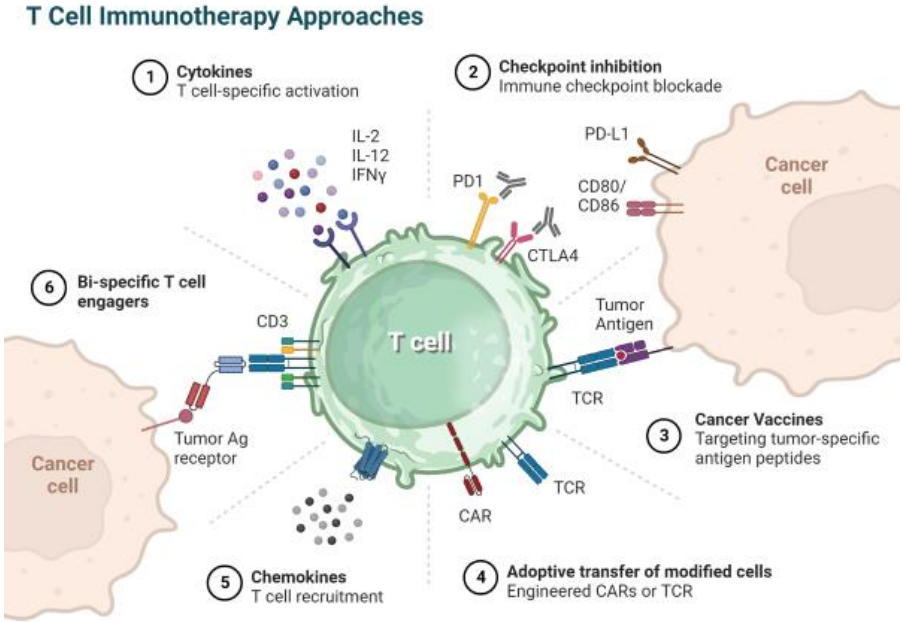

FIGURE 6. - Cancer Immunotherapy

Other incidents, such as heart disease, heart fibrosis, myocarditis, and abrupt cardiac failure, were described with anti-CTLA-4 or anti-PD-1 treatment individually. On the other hand, fatal coronary artery disease linked with myositis was seen with combination therapy, but it was not very common [32] [38].

2.12 TAKING PREVENTATIVE MEASURES AGAINST HEART DISEASE AND LOOKING FORWARD

It may not always be feasible to reverse specific effects of cancer pharmacotherapies. Current research on the management and monitoring of cardiotoxicity and the many adverse effects associated with both contemporary and traditional therapies has shown considerable promise. Dexrazoxane, a very promising cardioprotective drug, has shown efficacy in mitigating both acute and chronic cardiotoxicity resulting from anthracycline treatment. Dexrazoxane has shown the ability to disrupt iron-dependent redox processes, thereby diminishing reactive oxygen species generated by doxorubicin. Dexrazoxane directly inhibits topoisomerase IIβ, consequently obstructing anthracycline binding and the formation of DNA double strand breaks [31] [39,40].

Nonetheless, the efficacy of Dexrazoxane in mitigating anthracycline-induced cardiotoxicity has been limited in clinical applications due to significant side effects. A recent clinical trial shown that Dexrazoxane, when combined with

DOX, led to increased instances of bone marrow suppression, a greater frequency of febrile neutropenia episodes, and necessitated dosage reductions. The pursuit of innovative protection against cardiotoxicity in pharmaceuticals is more critical and urgently required[31] [41].

Treatment methods used either before, subsequent, or both prior and subsequent to cancer therapies have shown efficacy in addressing specific risk factors for cardiotoxic effects, including heart failure. The use of beta blockers, angiotensin-converting enzyme inhibitors, angiotensin inhibitors, and mineralocorticoid receptor antagonists has shown encouraging outcomes in the prevention of heart injury and is a subject of current enquiry. BBs has antioxidant characteristics and were used for chemotherapy-induced left ventricular ejection fraction (LVEF) and other forms of systolic left ventricular dysfunction. Carvedilol, a widely used drug among the new generation beta-blockers, had significant antioxidant properties and enhanced protective effects against anthracycline-induced cardiomyopathy [38]. A recent investigation indicated that ACE inhibitors and beta-blockers had beneficial benefits in avoiding cardiotoxicity and enhancing survival in breast cancer patients undergoing treatment with trastuzumab and/or anthracyclines. Furthermore, beta-adrenergic antagonism with nebivolol, metoprolol, lisinopril, and others has been shown to be efficacious for cardiomyopathy [42]. Nonetheless, data about some beta-blockers exhibiting advantageous cardioprotective benefits in individuals with left ventricular ejection fraction (LVEF) remain contentious [37] [43], as shown in figure 7.

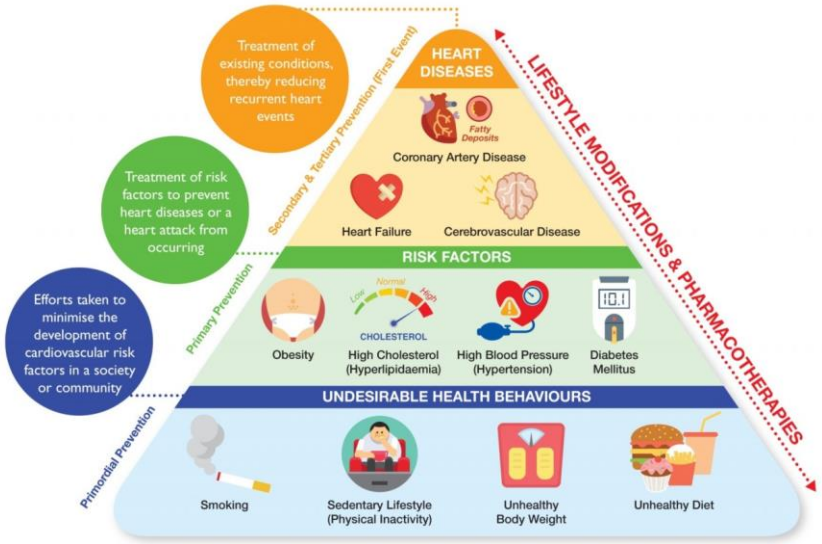

FIGURE 7. - Preventive Cardiology

This article presents an extensive review of the prevalence of cardiotoxicity induced by frequently utilized chemotherapeutic and immunotherapeutic agents, vulnerable genes, and radiation therapy, as well as the potential protective effects of antioxidants and other interventions to address anticancer cardiotoxicities in the future. Cardiotoxicity is a significant adverse effect of cancer treatments and a key obstacle to surviving. Nevertheless, contemporary cancer sufferers ought not to become future cardiovascular disease patients. Recent study has illuminated optimism, highlighting the need of early prevention. Ongoing study and discourse will enhance our literature on cardiotoxicity, paving the way for better treatment solutions. Additional research into alternative therapies and the growing knowledge of contemporary technology for screening and identifying at-risk individuals will aid in developing and accessing various modalities for cancer treatment. Furthermore, this review had been addressed the deficiencies in comprehending cardiotoxicity and investigate other research pathways that are often neglected.

3. CONCLUSION

This review on cardiotoxicity generated by anticancer therapies highlights the considerable problem presented by circulatory issues resulting from cancer treatments. As progress in cancer treatments improves survival rates, the simultaneous danger of cardiotoxicity requires a comprehensive strategy for patient care. The results underscore the significance of early recognition, surveillance, and cardioprotective measures to alleviate detrimental impacts on heart health. Future research must clarify the causes of cardiotoxicity, identify vulnerable individuals, and formulate tailored approaches to improve the safety and effectiveness of cancer treatments. A thorough comprehension of the connection between oncology and cardiology is crucial for enhancing patient outcomes and elevating the quality of life for cancer survivors.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest

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