CARDIOTOXIC EFFECT OF CHEMOTHERAPEUTIC AGENTS

Pooja Babbar[1*], D Lokanatha[1], Linu Abraham Jacob[1], M C Suresh Babu[1], KN Lokesh[1], AH Rudresha[1], LK Rajeev[1], Smitha Saldanha[1], GH Abhilash[1], Amit Pandey[1]

[1*,1] Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka 560029, India.

Vinay Kakkar [2]

Department of Orthopaedics, Swami Dayanand Hospital, New Delhi, Delhi 110095, India.[2]

Abstract

One of the most promising problems associated with the use of chemotherapeutic agents for cancer is cardiac toxicity. The root cause of multiple cardiac toxicity disorders such as left ventricular failure, pericarditis, myocarditis, myocardial ischemia, arrhythmias, thromboembolism, prolongation of QT and hypertension are the antineoplastic agents.Anthracyclines, alkylating agents, tyrosine kinase inhibitors, antimetabolites and HER2-directed therapy are some major medications that can induce cardiotoxicity. A detailed literature survey on different chemotherapeutic agents for cancer has been carried out.The present review and analysis address cardiovascular risks, potential mechanistic mechanisms of chemotherapy-induced cardiotoxicity and cardio-protective agents used in chemotherapy for the treatment of cancer.

Keywords: Anticancer:Anthracycline:Cardiotoxicity: Chemotherapy.

Introduction

Recent advances in cancer therapy have resulted in marked increases in cure rates in the last few decades. The advent of chemotherapy has greatly improved the outcome of cancer patients, and is a crucial factor in the care and management of different tumors.But there are many harmful side effects associated with chemotherapy, which significantly restrict its use[1]. Due to its adverse effect on prognosis and quality of life, cardiac toxicity is by far the most growing problem associated with the implementation of different groups of chemotherapeutic agents[2].An undesirable consequence is that the structure and function of normal cells in and around the heart may be destroyed by a chemotherapy agent. Cardiomyopathy, congestive heart failure, pericarditis, myocarditis, acute coronary syndromes, etc. are other forms of cardiac toxicity from cancer chemotherapy besides cell death.A significant reason for mortality and morbidity in patients has been shown to be chemotherapy-induced cardiac dysfunction [3-4]. As per the concept of cardiotoxicity by the National Cancer Institute (NCI), it says that 'It is the toxicity that affects the heart'. This description requires a direct drug effect on the heart.In addition, an indirect effect is often added to or can be triggered by thrombotic events due to increased variations in haemodynamic flow[5]. The NCI also recommends the Standard Adverse Events Terminology Criteria (CTCAE) that describes severity-based Left Ventricular Dysfunction and Heart Failures ranging from **grade 1** to **grade 5**.

Grade 1	• Asymptomatic elevations in biomarkers or abnormalities on imaging.
Grade 2	• Symptoms with mild and moderate exertion.
Grade 3	• Severe or medically significant but not immediately life threatening.
Grade 4	• Severe and life threatening symptoms requiring hemodynamic support
Grade 5	• Death

Figure 1 Grades of Left Ventricular Dysfunction and Heart Failures

Specific and variable degrees of direct (e.g., arrhythmias, hypertension, heart failure, ischemia, myocardial toxicity)[1,6-8] as well as indirect (e.g., adverse lifestyle changes) sequential and incremental cardiovascular insults[6] are also associated with existing chemotherapy anti-cancer treatment. The American College of Cardiology/American Heart Association (ACC/AHA) 2013 defines the level. A heart failure for patients with a high risk of heart failure after undergoing stage D chemotherapy without systemic heart disease (refractory HF), [3, and 9].A variety of recommendations have been released in recent years, including Ann Oncol (2011)[10], European Society for Medical Oncology (ESMO) in 2012 [11], the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) in 2014 [12], the European Society of Cardiology in 2016 and the American Society of Clinical Oncology (ASCO) in 2017 to guide practitioner in identification and treatment of cardiac dysfunction from cancer therapy[13-14].

Cardiac toxicity is known to have a high prevalence with respect to anticancer therapy[15]. The frequency of heart failure remains in the range of 1% to 5% and the asymptomatic drop in left ventricular activity is in the range of 5% to 20%. This adverse effect occurs during chemotherapy and could be a dose limiting factor compromising tumor response in the treatment of cancer[16].There are different novel selective agents for many cancers that have been clinically tested and confirmed for anti-tumor therapies but have some adverse cardiovascular effects[7,17-19]. The present analysis therefore focuses on the mechanistic mechanisms and identifies different possible chemotherapeutic agents that can be administered to patients, but may be at risk of cardiovascular complications.

2. Cardiovascular Complications from cancer therapy

Heart disease and cancer are the primary causes of death worldwide. The anti-neoplastic's cardiac toxicity is, though not limited to, left ventricular dysfunction, myocardial ischemia, arrhythmias, pericarditis, myocarditis, thromboembolism, QT prolongation and hypertension. Asymptomatic diastolic dysfunction (ADD), a common condition observed in many cancer survivors, is found as the earliest apparent cardiac abnormality [20-21]. **Figure 2** offers a diagrammatic illustration of cardiovascular problems associated with chemotherapeutic agents.

Cancer therapy-related cardiovascular complications are primarily classified into three groups, such as vascular disorders, cardiac structural concerns, cardiac dysfunction and heart

failure. Atherosclerosis, arterial thrombosis, hypertension, deep venous thrombosis, or pulmonary embolus is vascular problems, whereas pericardial effusion, pericardial constriction, valvular heart disease, and conduction system disease are part of a cardiac structural problem. Anthracycline, antiangiogenic therapy, trastuzumab, radiation therapy, and restrictive cardiomyopathy are associated with cardiac disease and heart failure. **Table 1** provides the chemotherapeutic agent that induces cytotoxic syndromes such as myocardial depression, ischemia, hypertension, hypotension, etc.
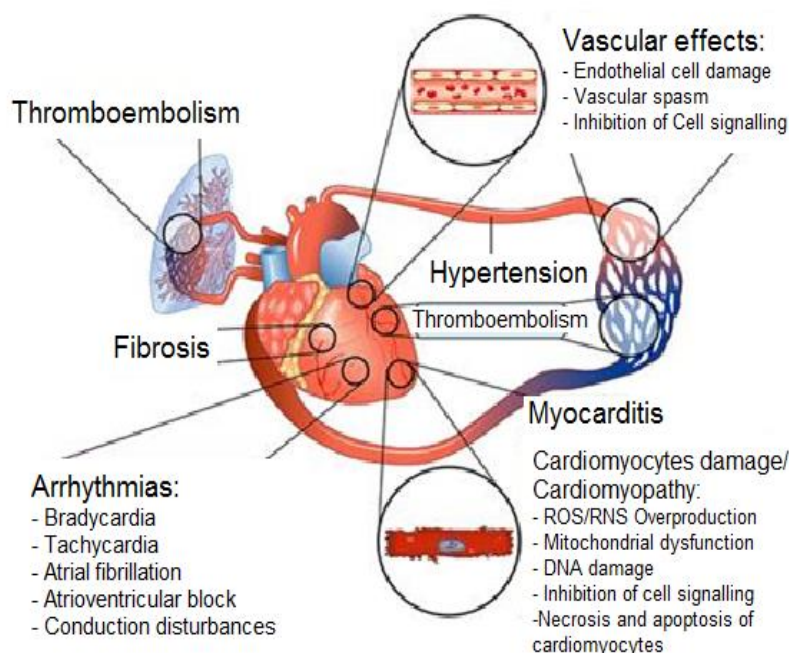

Figure 2: Diagrammatic representation of cardiovascular complications linked to chemotherapy agents

Table 1:Chemotherapeutic Agents with Cardiotoxic Syndromes

Cardiotoxic Syndromes Associated with Chemotherapeutic Agents				
Myocardial depression	**Ischemia**	**Hypotension**	**Hypertension**	**Other toxic effects**
Anthracyclines	5-FU	Etoposide	Bevacizumab	Cardiac tamponade/ endomyocardial fibrosis/ busulfan
Mitoxantrone	Cisplatin	Paclitaxel	Cisplatin	Hemorrhagic myocarditis/ cyclophosphamide
Cyclophosphamide	Capecitabine	Alemtuzumab		Bradyarrhythmias/ paclitaxel/ thalidomide
Trastuzumab	IL-2	Cetuximab		Raynaud phenomenon/ vinblastine
Ifosfamide		Rituximab		Autonomic neuropathy/ vincristine
Tretinoin		IL-2		QT prolongation or torsades de pointes/ arsenic trioxide/
		Denileukin		Pulmonary fibrosis/ bleomycin
		Interferon		
		Tretinoin		

3. Cardiotoxic chemotherapeutic agents

The cardiotoxicity caused by particular groups of chemotherapy drugs has been illustrated by several studies. **Table 2** provides the Cardiovascular Manifestation of widely used chemotherapeutic agents.

Table 2: Cardiovascular Manifestation of commonly used chemotherapeutic agents

Category of drugs	Chemotherapeutic Agents	Cardiovascular Manifestation
Anthracycline agents	Doxorubicin, Daunorubicin, Epirubicin, Idarubicin, Mitoxantrone	Arrhythmia, LV dysfunction, CHF, myopericarditis
Alkylating agents	Cyclophosphamide, Ifosfamide, Busulfan, Cisplatin, Mitomycin	CHF, arrhythmias, hypertension,myopericarditis, thromboembolism
Angiogenesis inhibitors	Thalidomide, lenalidomide, pomalidomide	Bradycardia, thromboembolism, hypertension
Antimetabolites	5-fluorouracil, capecitabine, cytarabine, methotrexate, fludarabine	CHF, arrhythmias, coronary vasospasm, myocardial ischemia, myopericarditis
TKI	Imatinib, Dasatinib, Erlotinib, Lapatinib, Lenvatinib, Nilotinib, Pazopanib, Ponatinib, Sorafenib, Vandetanib, Sunitinib	CHF, QT prolongation, hypertension, myocardial ischemia, thromboembolism
Antiandrogens	Abiraterone, Degarelix, Enzalutamide	Hyper-lipidemia, thromboembolism, QT prolongation
Antiestrogens	Tamoxifen, Letrozole	Thromboembolism, hypertension
Antimicrotubule	Paclitaxel,	CHF, myocardial ischemia,

agents	Docetaxel, Etoposide, Teniposide, Vincristine, Vinblastin	QT prolongation, Bradycardia, Hypotension
HER2/ Neu receptor blockers	Trastuzumab, Pertuzumab	Left ventricular dysfunction and CHF
Proteosome inhibitors	Bortezomib, Carfilzomib	CHF, Myocardial Ischemia
Histone deacetylase inhibitors	Romidepsin, Vorinostat	QT prolongation, thromboembolism
Miscellaneous	Bleomycin	Myopericarditis
	Interferone	Hypertension, hypotension, myocardial ischemia
	Interleukin-2	Arrhythmias, hypotension, myocardial ischemia
	Tretinoin	CHF, hypotension
	Arsenic trioxide	QT prolongation

CHF- Congestive Heart Failure; LV- Left Ventricular; TKI-Tyrosine Kinase Inhibitors

In the present study, some essential chemotherapeutic agents that induce cardiotoxicity have been discussed in the following section.

4. Cardiotoxicity induced by Anthracycline agents

Anthracyclines were identified half a century ago and are the class of antibiotics used to address a wide variety of cancers, including leukemia, lymphoma, sarcoma, and breast cancer[22]. Anthracyclines are the most active anticancer drugs that are derived from the bacterium Streptomyces [23].Anthracyclines are an essential class of chemotherapeutic agents, such as doxorubicin, daunorubicin, epirubicin, mitoxantrone and idarubicin. As an anticancer agent, the dose-dependent cardiac toxicity caused by anthracyclines limits their efficacy. Anthracycline is associated with cardiomyocyte damage & death, resulting in LV dysfunction & heart failure. Different forms of cancer associated with anthracycline chemotherapy are represented in Table-2. Risk factors linked to anthracycline-induced cardiac toxicity include age, cumulative dosage, radiation therapy, concomitant chemotherapy, etc.Although doxorubicin has become one of the most potent chemotherapeutic agents, its use has been complicated by developing heart failure [38]. In a retrospective study conducted by Von Hoff and colleagues, 2.2 per cent of patients were

developed clinical signs or symptoms of congestive heart failure [39].

4.1. Mechanisms of Cardiotoxicity

Based on the impact of the agent on cardiomyocytes, chemotherapeutic cardiac toxicity can be classified as type 1 or type 2 [40-41]. Form I cardio-toxicity is caused by cardiomyocyte death, typically caused by anthracyclines and chemotherapeutics, by apoptosis or necrosis, which is irreversible.In relation to cell death, type II cardio-toxicity is reversible in nature and is caused by cardiomyocyte dysfunction, as in the case of type I[42]. Understanding the etiology of cardiac anthracycline toxicity enables preventive strategies to be developed to combat the production of permanent cardiac injury.The hypothesis that anthracyclines interfere with the redox cycle is generally accepted, resulting in DNA damage due to the formation of reactive oxygen species (ROS)[43]. However, accurate cardiac toxicity caused by anthracycline is still unknown. Topoisomerase-2 has recently been proposed as the primary cardiotoxicity mediator [44-45].

4.1.1. Cardiotoxicity through Reactive Oxygen Species

ROS production in heart cell mitochondria is the molecular basis of cardiac drug toxicity. The quinone moiety of anthracyclines is subject to a uniform reduction of many cellular oxidoreductases to a semiquinone radical. This is primarily achieved with dehydrogenase NADH in myocardial cells (complex I), which involves enzyme pathways affiliated with electrons' mitochondrial transport chain [46]. Semiquinone auto-oxidizes and activates the parent anthracycline with a superoxide anion in the presence of molecular oxygen [47]. The non-enzymatic pathway makes a self-perpetuating redox loop that contributes to superoxide anion accumulation. Free cellular iron and possible ferrous-ferrous molecular iron cycling [48] can also increase ROS concentrations. The toxic radical and reactive nitrogen species are formed by doxorubicin-iron complexes, leading to increased nitrosative stress and mitochondrial dysfunction [49].

4.1.2 Cardiotoxicity through Topoisomerase 2β

Top-regulated topologic shifts in DNA topoisomerase (Top) cause temporary single or double-stranded breaks during DNA replication, transcribing, recombination, and chromatin reshaping [50]. Top2 is expressed as Top2 α and Top2β isoenzymes in humans [51]. Top2 α is the most prevalent of the two isoenzymes and is highly expressed in proliferating nonmalignant and malignant cells. It is essential for chromosome segregation, and its expression fluctuates through the cell cycle, particularly during G2/M phases [52]. Topoisomerase-2β is more common in dormant cells, such as adult cardiomyocytes, and its expression remains constant throughout the cell cycle .

Doxorubicin exerts its anti-cancer effect by interpolating DNA. Topoisomerase 2 and DNA bind to doxorubicin, which forms the Top2-doxorubicin-DNA ternary complex and leads to a break in double-stranded DNA. The ternary complex, bound to Top2α, prevents the cell cycle in G1/G2 and

inhibits DNA replication and contributes to apoptosis [53] as seen in malignant cell proliferation on the other hand, the oxidative metabolism-reduced peroxisome proliferator-activated receptor (PPAR) in adult mammalian cardiomyocytes, micro-dysfunction, with impaired calcium handling, βadrenergic signalization and increased apoptosis, is suppressed when bound to Top2β and results in mitochondrial dysfunction. [54] Doxorubicin does not attach directly to DNA without Top2β [53]. Animal studies with Top2β knockout mice have shown that the lack of Top2β protects against doxorubicin-induced cardiac toxicity, partially due to reduced mitochondrial dysfunction [51, 56].
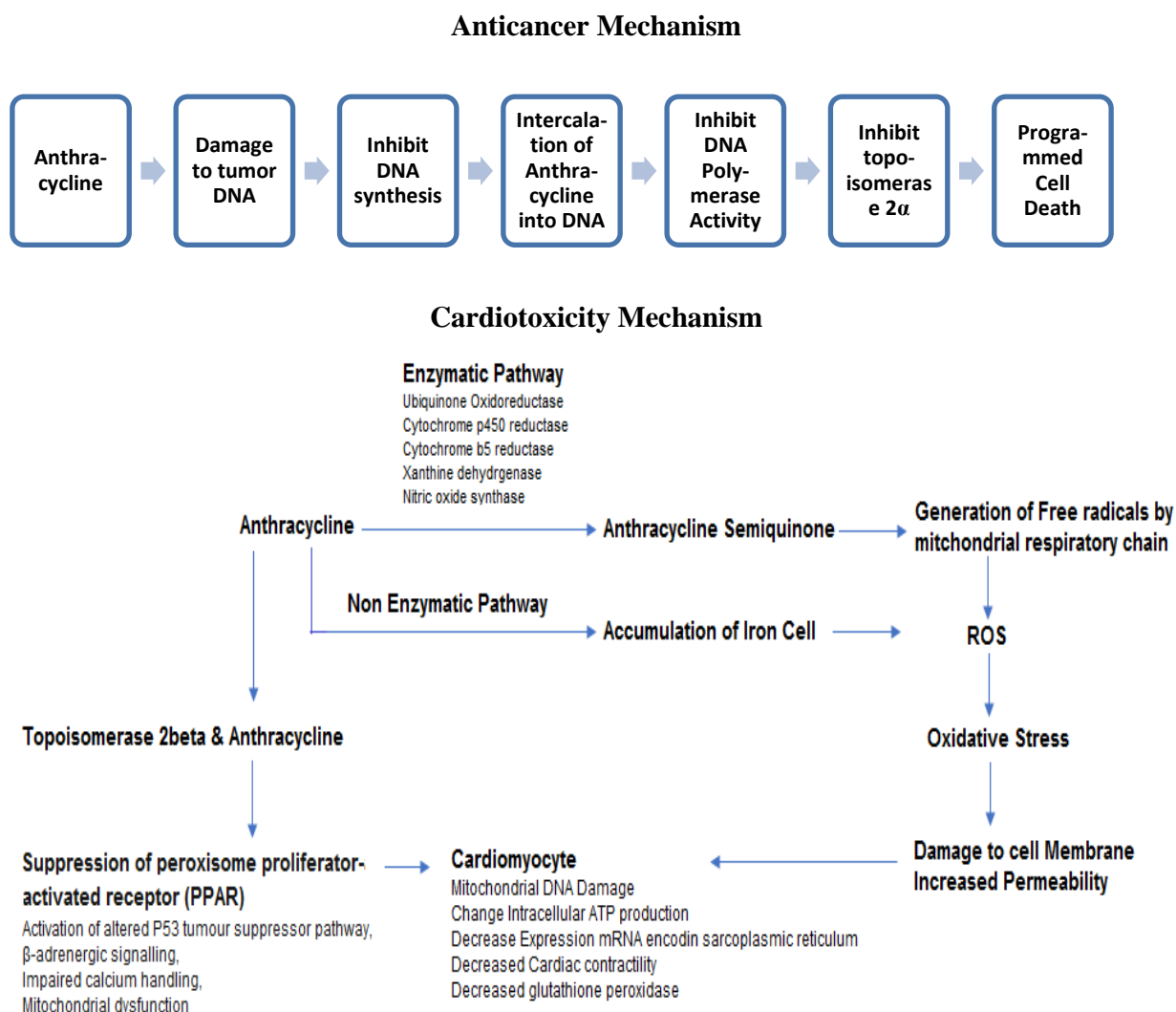
Anticancer Mechanism

Anthra-cycline → Damage to tumor DNA → Inhibit DNA synthesis → Intercala-tion of Anthra-cycline into DNA → Inhibit DNA Poly-merase Activity → Inhibit topo-isomerase 2α → Progra-mmed Cell Death

Cardiotoxicity Mechanism

Enzymatic Pathway
Ubiquinone Oxidoreductase
Cytochrome p450 reductase
Cytochrome b5 reductase
Xanthine dehydrgenase
Nitric oxide synthase

Anthracycline → Anthracycline Semiquinone → Generation of Free radicals by mitchondrial respiratory chain

Non Enzymatic Pathway
→ Accumulation of Iron Cell → ROS

Topoisomerase 2beta & Anthracycline

Oxidative Stress

Suppression of peroxisome proliferator-activated receptor (PPAR)
Activation of altered P53 tumour suppressor pathway,
β-adrenergic signalling,
Impaired calcium handling,
Mitochondrial dysfunction

Cardiomyocyte
Mitochondrial DNA Damage
Change Intracellular ATP production
Decrease Expression mRNA encodin sarcoplasmic reticulum
Decreased Cardiac contractility
Decreased glutathione peroxidase

Damage to cell Membrane Increased Permeability

Figure 3: Anticancer and cardiotoxicity mechanism of Anthracycline

4.2. Treatment of anthracycline cardiotoxicity

For the treatment process, multiple medications are used, such as ACE inhibitors or angiotensin receptor blockers (ARB), beta-blockers and CHF therapy. The use of these agents will lead to the stabilisation of the LV systolic function[57]. Only beta-blockers of nebivolol or carvedilol may be used, but cardiovascular toxicity of anthracycline may be used with any ACE inhibitor or ARB.Domain experts preach that better care will often result from an early diagnosis. This procedure also requires a high degree of expenditure[58]. Relentless control of LVEF that is

non-invasive in nature can be a safer cost-effective way of preventing CHF [59]. An iron chelator, Dexrazoxane, reduces anthracycline cardio-toxicity. However, its use in clinical practice has been limited by adverse effects, including myelotoxicity, and by concerns regarding leukemia. Only in patients receiving >300 mg/m2 of doxorubicin[60] is its use allowed.

5. Cardiotoxicity induced by Alkylating agents

It has been found that cardiotoxicity has been associated with alkylating agents such as busulfan, carmustine, cisplatin, chlormethine, cyclophosphamide, ifosfamide and mitomycin [61].

5.1. Cyclophosphamide

Cyclophosphamide-associated cardiotoxicity is rare in patients treated with high-dose chemotherapy, but can cause severe obstacles [62-64]. Cyclophosphamide is an alkylating nitrogen mustard, an antineoplastic agent that is increasingly used to treat different cancer forms and to exhibit immunomodulatory activity.Important cardiotoxicity can involve fatal hemorrhagic myocarditis that may occur as a result of higher drug doses[65]. This was supported by the 2009 Katayama and co-workers study[66], which revealed a case of a 59-year-old male with abdominal mass containing large B cell lymphoma who received high-dose cyclophosphamide-containing chemotherapy.Just5 days after cyclophosphamide administration, the patient developed congestive heart failure.

CHF or myocarditis or both are clinical manifestations of cardiotoxicity caused by cyclophosphamide, leading to death [62, 67-68]. Although chest pain, pericardial friction and rhythm are associated with pericarditis[68], cyclophosphamide-associated cardiotoxicity pathogenesis involves toxic endothelial damage caused by cyclophosphamide and results in the release of toxic metabolites, resulting in damage to myocytes, interstitial hemorrhage and/or edema[62-63].With the extravasation of toxic metabolites, proteins and erythrocytes, cyclophosphamide metabolized by CYP450 in the liver and the metabolites thus formed are expected to cause oxidative stress and direct endothelial capillary harm.The endothelial cells are ruptured due to the release of toxic metabolites, causing direct damage to the myocardium and capillary blood vessels, leading to interstitial hemorrhage, edema, damage to myocytes, and development of microthrombi[69-70]. Severe cardiac toxicity is believed to be ischaemic damage caused by the development of intracapillary microthrombi.Such invectives are clinically manifested as arrhythmias and acute heart failure. Interstitial transudation and endothelium damage can decrease electrical activity and decrease the QRS complex, enabling systolic left ventricular function[71].The effects of coronary artery vasospasm in myocardial ischaemia are also demonstrated by cardiotoxicity caused by cyclophosphamide.

5.2. Ifosfamide

Ifosfamide (IFS) is an alkylating oxazaphosphorine used against soft tissue sarcomas and lung carcinomas that is structurally related to cyclophosphamide [72-74]. High-dose ifosfamide can trigger serious side effects, but with regard to myocardial depression and malignant arrhythmias,

they are usually reversible in nature[75].The cardiotoxic effect of Ifosfomide was first suggested by Kondylis et al in 1989[76]. The author documented acute cardiac arrhythmias with unusual ST-T wave alteration created during IFS treatment at a higher dose. They are reversible after the medication is removed.The study also indicated that antiarrhythmic therapy might be required for arrhythmia conversion. Irreversible and refractory arrhythmia can be caused by re-exposure to IFS.

Cardiac toxicity can be associated with the delayed elimination of Ifosfamide's cardiotoxic metabolites. This is focused on the steady increase in serum creatinine found before CHF occurs. Fluid and acid-based electrolyte imbalance can be found in these patients due to the amount of fluid and sodium administered by chemotherapy and ifosfamide assisted tubular defects, and thereby inducing myocardial decompensation. If the patient has previously been exposed to doxorubicin, this can potentiate cardiotoxicity with ifosfamide[61, 77-78].

5.3. Carmustine

The synthetic derivative of nitrosourea used as an alkylating agent for the treatment and control of refractory Hodgkin's disease [79], non-lymphoma [79-80] Hodgkin's and multiple myeloma [81-82] is Carmustine or BCNU (bis-chloroethylnitrosourea). Carmustine-related cardiac toxicity is not well described and the occurrence is very rare, but substernal chest pain can be caused by both arms, hypotension, and sinus tachycardia. The manifestation of a current myocardial infarction may not be indicated by cardiac enzymes and ECG monitoring. Depression of the 1 to 2mm ST segment and Sinus tachycardia can be found on the ECG.Hypotension, which can be treated with IV fluids and inotropes, can be marked during or a few hours after the completion of the infusion. Myocardial ischemia occurrence was observed with a high dose infusion of carmustine (approximately 600 mg/m2) [83-84].

The mode of action involved in BCNU's cardiotoxicity is still unidentified. Different clarifications were proposed and suggested by the various investigators. The dramatic reduction in blood flow secondary to severe vasodilatation may be an explanation for the mechanism.Some experimental data have shown various cardiovascular modifications fall in arterial blood pressure (reduction of 31 mm Hg in systolic pressure and of 26 mm Hg in diastolic pressure), extreme flushing due to high-dose BCNU infusion [85] and tachycardia. This indicates that these phenomena can be more severe in some cases and lead to the occurrence of symptomatic heart dysfunction.Myocardial ischemia has been shown to be linked to a drop in blood pressure in different cases reported in the literature. In one of the cases complicated by fatal myocardial necrosis, a drop in blood pressure to 50 mmHg was observed [86].

5.4. Mechlorethamine

A type of nitrogen mustard alkylating agent that plays a primary role in the early stages of skin disease is mechlorethamine or chlormethine. Since 1959, it has been investigated in Mycosis fungoides (cutaneous T-cell lymphoma) for its efficacy[87].Liner et al 2018[88] indicated that mechlorethamine gel was safe and efficient in the early stages of the Mycosis fungoides type of

cutaneous T-cell lymphoma relative to other nitrogen mustard formulations. Cardiac side effects caused by mechlorethamine at regular doses are rare.However, when administered at a higher dose of 33 mg/m2 with autologous bone marrow transplantation for the treatment of advanced malignant melanoma, greater cardiotoxicity was observed [61,89]. The literature survey indicated that mechlorethamine-related cardiotoxicity is very rare.The adverse effect on heart tissue can be due to mechlorethamine in some cases, and the extent of the effect is still uncertain.

5.5. Buslfan and Melphalan

Since 1959, Busulfan has been an alkyl sulfonate class of anti-neoplastic alkylating agent used in the treatment of chronic myelogenous leukemia when administered orally. It is a parenteral myeloablative agent used in hematopoietic cell transplantation preparation.Busulfan cardiac toxicity is very rare and only endocardial fibrosis [90] and pericardial fibrosis [91] have been reported in two cases during the treatment of chronic myeloid leukemia.

Melphalan is a drug used for chemotherapy in the treatment of melanoma, myeloma, breast cancer, and sarcoma. The high dose of melphalan may cause cardiac toxicity that contributes to atrial fibrillation (AF, 6.6-11%) and supraventricular tachycardia during care. The most arrhythmogenic chemotherapeutic agent used in ASCT is known to be Melphalan. There are noted risk factors responsible for supraventricular tachycardia (SVT) for elevated age over 60 years, higher baseline creatinine, greater left atrium capacity, and prior cardiac comorbidities [92-93].The electrocardiogram indicates an acute onset of ventricular rhythm with atrio-ventricular (AV) dissociation after administration of 200 mg melphalan. The successor ECG displays complex ventricular rhythm at 4 hours, 8 hours, and 12 hours after initiation of administration of melphalan [94].

Tandem autologous hematopoietic stem cell transplantation treatment, which is used with high-dose cyclophosphamide accompanied by two myeloablative cycles of melphalan[95], can treat multiple myeloma.Both high-dose cyclophosphamide chemotherapy agents and two dosages of myeloablative melphalan can exert mild and partially reversible cardiotoxic side effects, but with chronic and clinically silent effects[95-96]. During therapy, it was found that heart failure is neurohormonally triggered. The deterioration of left ventricular diastolic function and the incidence of functional mitral regurgitation have been found in Doppler echocardiography studies[96].

6. Cardiotoxicity induced by Cisplatin

Cisplatin is referred to as cis-diamminedichloroplatin (II), a cytotoxic antineoplastic alkylating agent used specifically for the treatment of different forms of cancers, such as germ cell tumors, carcinomas, sarcomas, and lymphoma [97,98]. Cisplatin is used to treat a number of body cancers, including lung cancer, breast cancer, cancer of the head and neck, cancer of the cervix, testicular and bladder cancer [99]. Ototoxicity, neurotoxicity, nephrotoxicity and gastrointestinal toxicity are the major adverse acts of cisplatin (>50mg/m2). Cardiac toxicity caused by cisplatin is

unusual and the incidence remains unknown. Jakubowski and Kemeny[100] found that 6 percent of the patients had an incidence of cardiac toxicity. As stated in different literature, certain cardiotoxic manifestations of cisplatin chemotherapy have been listed as follows: -

1. Cisplatin induced angina [101],

2. Heart failure [102],

3. Thromboembolic events [103],

4. Acute myocardial infarction [104],

5. Autonomic cardiovascular dysfunction [103],

6. Hypertension [105]

7. Hypotension [106],

8. Pericarditis,

9. Myocarditis,

10. Congestive cardiomyopathy [102, 107].

Hu et al 2018[108] diagnosed a case of cervical squamous cell carcinoma and confirmed that cardiac toxicity could be associated with administration of cisplatin. The electrocardiogram revealed first-degree atrioventricular block and ST-segment depression of 0.05 mv on leads II, III, and V3-5.Neither neither the cardiac markers nor the natriuretic peptide N-terminal pro-B-type (NT-pro BNP) have been elevated. The laboratory study and physical examination showed that cervical cancer did not develop. Whereas Martínez-Mateo et al 2017[109] indicated that Cisplatin-induced LV systolic dysfunction and bradycardia is typically an acute adverse effect and is reversible after removal of drugs.

Cardiac toxicity has been shown to be consistent with cisplatin therapy. Cardiotoxicity also results in leaks from the cardiac myocytes of lactate dehydrogenase and reatine kinase. These could be secondary processes that may result from lipid peroxidation caused by cisplatin or cardiac membranes[110]. Previous studies have shown that cisplatin-based chemotherapy, backed by decreased antioxidant production, can induce oxidative stress by increasing ROS production. It has been shown that the development of free radicals leading to oxidative stress shows the cardio-toxic effects of cisplatin [111].

7. Antimetabolites

Capecitabine, gemcitabine and 5-fluorouracil (5-FU) are known to be the antimetabolite class of fluoropyrimidine antineoplastic agents used in the treatment of different tumors. After several days of therapy, 5- FU and its primary metabolite can also cause cardiotoxicity [112-113]. The incidence of cardiotoxicity caused by 5-FU ranges from 0 to 35 percent, while the rate of mortality is 2-13 percent.Intravenous 5-FU administration has been reported to have a short half-life, but active metabolites are concentrated in cancer and cardiac cells, resulting in prolonged drug exposure [114-116]. In particular, capecitabine is transformed into its active form in tumors [117-120].As in the context of coronary artery disease, cardio-toxicity may be due to the enzyme

involved in the conversion of capecitabine to 5-FU expressed both in atherosclerotic plaques and in cancer cells.

Myocardial ischemia is said to pose the highest risk of cardiotoxicity caused by fluoropyrimidine [121,122]. The cardiac stress test for silent ischemia has been reported to be in the range of 6–7% of 5-FU-treated patients [123].NO inhibition [124-125], higher endothelial thrombogenicity [126], increased ROS/RNS generation [127] and senescence [128], and DNA-RNA damage may be the probable mode of action that may be involved in cardiotoxicity induced by 5-FU and its metabolites. In endothelial cells and cardiomyocytes, the 5-FU can induce oxidative stress.These medications induce eNOS dysregulation, which is the upregulation of the activation of protein kinase-C and endothelin-1. This effect results in independent and dependent vasoconstriction of the endothelium and finally coronary spasm [129-130].

8. Trastuzumab induced cardiotoxicity

HER1, HER2, HER3 and HER4 are the epidermal growth factor, receptor family. These are tyrosine kinases that play an essential role in cell growth and are frequently upregulated in various carcinomas, including breast carcinoma [131]. In breast cancer, gene amplification of HER2, which is known as a HER2-positive subtype, was shown to be approximately 20-30 per cent [132-134]. In 1998 the FDA approved trastuzumab as the first target agent for human epidermal growth factor receptor-2 (HER2) [135]. Multiple oncological disorders have been accepted for therapy, including HER2-positive, neoadjuvenating, metastatic gastric and metastatic brain cancers [136-138]. Trastuzumab has the binging site of the extracellular domain of HER2 at domain IV and leads by various pathways to initiate its tumor-suppressive actions including antibody-dependent cell-mediated cytotoxicity activation, HER2 receptor destruction, homodimerization and heterodimerization, HER2 extracellular domain cleavage inhibition, oncogenic cell signalling abrogation, and angiogenesis and DNA healing pathways down-regulation [136,139-140].

When Trastuzumab binds to HER2, the neuregulin-induced HER4 receptor inhibits its dimerization. Neuregulin-1 (NRG-1) initiates the cell survival pathway with a HER4 receptor that prevents apoptosis and retains cardiac function [141-142].As angiotensin II binds to its AT1 receptor, NADPH activation and the radical development of superoxide lead to increased oxidative stress. Additional doxorubicin treatment also enhances oxidative stress. This increase in oxidative stress contributes to activating the pathways that cause ASK-1 and N-terminal kinase (JNK) apoptosis and heart failure [143]. Figure 4 provides the schematic illustration
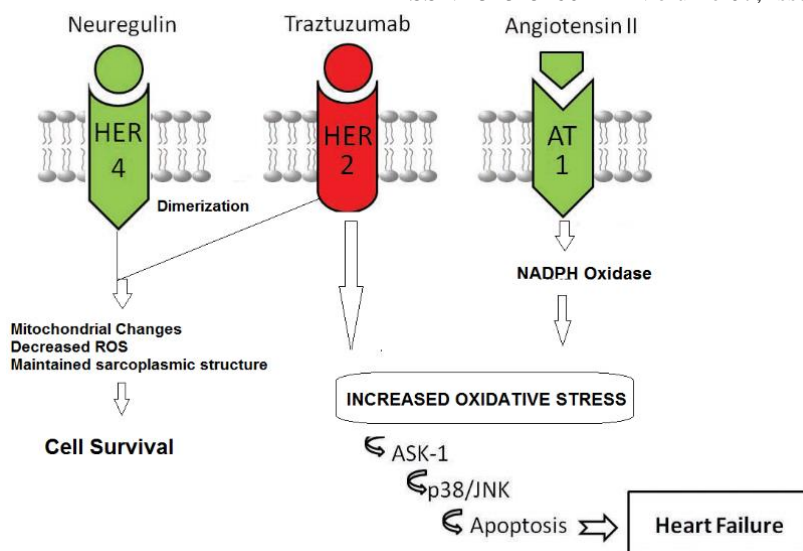
Figure 4. Schematic illustration of cell survival via signaling of Neuregulin and probable trastuzumab-induced mechanism of cardiotoxicity

The risk of developing cardiovascular complications remains increased in patients treated with trastuzumab, especially if they are prior anthracyclinical and are older than 50 years of age or have a previous heart disorder (ejection fraction <55 per cent) or if they experience a higher degree of BMI, HTN and renal abnormality. These patients are typically in anyone who needs care, including cardioprotective agents such as angiotensin receptor blockers, ACE inhibitors and b-blockers[144-146].

9. Tyrosine Kinase Inhibitors induced cardiotoxicity

The proteins whose activation leads to the phosphorylation of main substrates in the cell are essentially tyrosine kinases (TKs). There are mainly two forms of tyrosine kinases, as mentioned below—

A) Receptor Protein Kinases and

B) Non-Receptor Tyrosine Kinases [147].

The small molecules which obstruct the activity of the kinase are tyrosine kinase inhibitors. They have very high affinity with the TK binding sites of adenosine triphosphate (ATP) and function by inhibiting the transfer of one phosphate group from ATP to the residue of tyrosine. In both cancerous and non-cancerous cells, TKIs inhibit TKs [148].As a result, the effect of TKIs on normal tissue results in an adverse effect, such as cardio-toxicity. Sunitinib [149-150], dasatinib [151], and sorafenib [152-153] were approved for the majority of cardiotoxic kinase inhibitors, even after expressing adverse cardiac events (e.g., LV [LVD], HF, cardiac ischemia, and myocardial infarction), although these all were reported in patients during clinical trials too.

Dasatinib is one of the TKIs approved for treating chronic myeloid leukemia (CML) and acute lymphoblastic chromosome-positive leukemia (Ph+ ALL) disease Philadelphia. The clinical markers of cardiotoxicity were QT prolongation, CHF, LVD and myocardial infarction. The proposed mechanism for cardiotoxicity literature is the activation of the ER stress response that

leads to cell death [154-156]. Gefitinib is another TKI that increases the BNP and β-MHC levels and reduces the Alpha-MHC levels, contributing to cardiac hypertrophy leading to both caspase-3 and P53 apoptosis ultimately to myocardial infarction/ischemia. Sorafenib has been shown to pose a risk of myocardial infarction, QT prolongation, and high blood pressure by research. Protein inhibitions, vascular endothelium growth factor receptors, RG potassium canals and RAF/MERK/ERK[154-156] pro-survival pathways are all part of the expected mode of action for these side effects. Finally, Lapatinib is used to treat advanced or metastatic breast cancer. Lapatinib is a dual kinase inhibitor of both the endothelial growth factor (EGFR or ERbB1) and HER2 (ERbB2)[158]. In clinical tests, Lapatinib displayed signs of decreased left ventricular expulsion (LVEF) and QT prolongation. In the literature, these are identified as side effects of the ErbB2 target binding leading to mitochondrial apoptosis[154,156,159].

10. Cardioprotective agents

Several strategies for minimizing the risk of cardiotoxicity have been proposed and used. A combined dosage of a variety of drugs is most widely used: 550 mg/m2 for adriamycin, 600 mg/m2 for daunorubicin, 1000 mg/m2 for epirubicin, 1900 mg/m2 for zorubicin and 160 mg/m2 for mitoxantrone [160]. It is safer to use it in lower doses while other antineoplastic cardiotoxic medications are used or radiotherapy with mediastinum is used.

If anthracyclines are used in smaller amounts and in repeated doses, or if the infusion duration is extended to 48-96 hours, then the risk of cardiotoxicity, this can be mainly attributed to elevated plasma concentrations in the drug. 1st generation cardiotoxic derivatives of anthracyclines, such as idarubicin, epirubicin or mitoxantrone, have also been suggested to be used in fewer quantities and should only be used in the clinical setting. However, it is also shown that, at higher doses, second-generation anthracyclines can also induce cardiotoxicity [161]. Also in between many anthracyclines, the damage can be increased.

Several clinical trials identified substances that protect myocardium from the toxicity of anthracycline without reducing its antineoplastic activity[162]. E.g., at 20:1 or 10:1 doses of adriamycin, cardioprotective agents such as ICRF187 (dexrazoxane) can reduce the incidence of heart diseases by 30-50 per cent and at 10-15 per cent, anthracycline cardiopathy by the creative risk[163]. Some other studies have shown that high dexrazoxane doses (>900mg/m2) can counteract adriamycin and epirubicin's antineoplastic activity linked to improved overall detection of medication. It can also cause bone marrow toxicity, apart from that. Therefore, dexrazoxane is not commonly used in clinical planning but typically in patients who require extra doses of an anthracycline with a previous heart attack. Other products such as vitamin E, ascorbic acid, and different antioxidants have not yet shown a satisfactory cardioprotective impact in vivo[164].

Chemotherapy should be stopped immediately if there are signs of left ventricular dysfunction, and regular medical treatment for heart dysfunction should begin. There are diuretics, beta-blockers, inhibitors of ACE, and plans for periodic follow-up. Symptoms of heart dysfunction

will vanish if trastuzumab is discontinued. Cardiac treatment may be stopped if these signs vanish.

In the event of cardiotoxicity with trastuzumab, trastuzumab should be stopped indefinitely. For cardiotoxicity, there are no symptomatic anecdotes accessible. Trastuzumab was also found to be able to cause apoptosis in neoplastic cells. However, the presence of this problem has not yet been observed in the myocardium[165].

In order to find out whether there are any signs of ischemic cardiopathy, patients taking fluorouracil therapy require a cardiological examination before beginning the therapy. If the patient is diagnosed with ischaemic cardiopathy, the first large doses (greater than 800mg/m2) should be used for cardiological check-up after infusion.If the infused doses are low, cardiac ischaemic patients should be tested for cardiology after 2 weeks. If angina is detected in a patient, a stress test should be conducted. Alternative medicines may be required in patients with a history of cardiopathy or with symptoms of fluorouracil cardiotoxicity.In certain cases, however, fluorouracil can seem essential; it should be administered with continuous ECG monitoring in a regulated setting, along with nitrogen and calcium antagonists. It may be beneficial to adjust the clinical technique, such as administering low weekly doses rather than constantly infusing [166].Given all of these precautions, fluorouracil can no longer be administered if toxicity rises at an alarming pace.

11. Conclusion

These recently developed chemotherapeutic agents offer tremendous benefits to patients with various types of cancer. Some of these agents are, however, directly associated with short-term and long-term intoxication. One of the severe problems of many anticancer agents is cardiotoxicity. Therefore, a subs-specialization called cardio-oncology has arisen in the medical fraternity.The aim of this sub-specialty is to research the impact on the human cardiovascular system of cancer drugs. It helps to detect cardiotoxicity early on. For a better understanding of the genetic, biochemical, and cellular mechanisms of cardiotoxicity, more research in this area is essential.Before beginning treatment, it can help recognize any potential cardiotoxicity and its resulting impact. It would also help personalize the therapeutic regimen based on the sensitivity of the tumor and the susceptibility of the patient to toxicity.

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