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A Comprehensive Review of Cancer Drug–Induced Cardiotoxicity in Blood Cancer Patients: Current Perspectives and Therapeutic Strategies

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Opinion statement

Cardiotoxicity has emerged as a serious outcome catalyzed by various therapeutic targets in the field of cancer treatment, which includes chemotherapy, radiation, and targeted therapies. The growing significance of cancer drug–induced cardiotoxicity (CDIC) and radiation-induced cardiotoxicity (CRIC) necessitates immediate attention. This article

intricately unveils how cancer treatments cause cardiotoxicity, which is exacerbated by patient-specific risks. In particular, drugs like anthracyclines, alkylating agents, and tyrosine kinase inhibitors pose a risk, along with factors such as hypertension and diabetes. Mechanistic insights into oxidative stress and topoisomerase-II-B inhibition are crucial, while cardiac biomarkers show early damage. Timely intervention and prompt treatment, especially with specific agents like dexrazoxane and beta-blockers, are pivotal in the proactive management of CDIC.

Introduction

Cancer drug–induced cardiotoxicity has emerged as a major obstacle in the cancer treatment timeline. While advances in tumor biology and the development of effective cancer treatments have been made, the potential for heart damage has emerged as a critical challenge. In the mid-twentieth century, the emphasis was mostly on surgery, and radiation therapy became important in management of localized disease. However, as efforts have shifted from organ-specific therapies to systemic approaches, none of these therapies has taken center stage. Researchers from numerous fields have collaborated throughout the years to develop more effective and targeted cancer treatments, which were initially based on empirical data (Fig. 1).

Platelets, red blood cells, and leukocytes are some of opportunistic biological materials found in the blood. Bone marrow acts as a factory, producing blood cells and releasing them into blood circulation. Disruption in development and growth of these blood cells impedes normal blood cell growth, which may result in blood cancer. The exponential growth of abnormal blood cells hinders the normal growth of blood cell growth, eventually leading to blood cancer [1]. The three main types of blood cancer are leukemia, lymphoma, and myeloma. According to National Cancer Institute (NCI), the 5-year relative survival rate for all types of leukemia is 65%.

Chemotherapy, radiotherapy, surgery, immunotherapy, and the novel molecular-targeted drug therapies are the mainstay cancer treatment options [2•]. Nowadays, we are able to cure approximately 70–80% children and adolescents with cancer [3]. Cardiotoxicity could result from a complex and intertwined cellular regulation process involving the cellular proliferation and cardiovascular physiology.

Cancer drug–induced cardiotoxicity (CDIC) and cancer radiation–induced cardiotoxicity (CRIC) are two of the most common clinical issues related to cancer treatment. Cardiac failure is the most common form of CDIC, but this also includes hypertension,

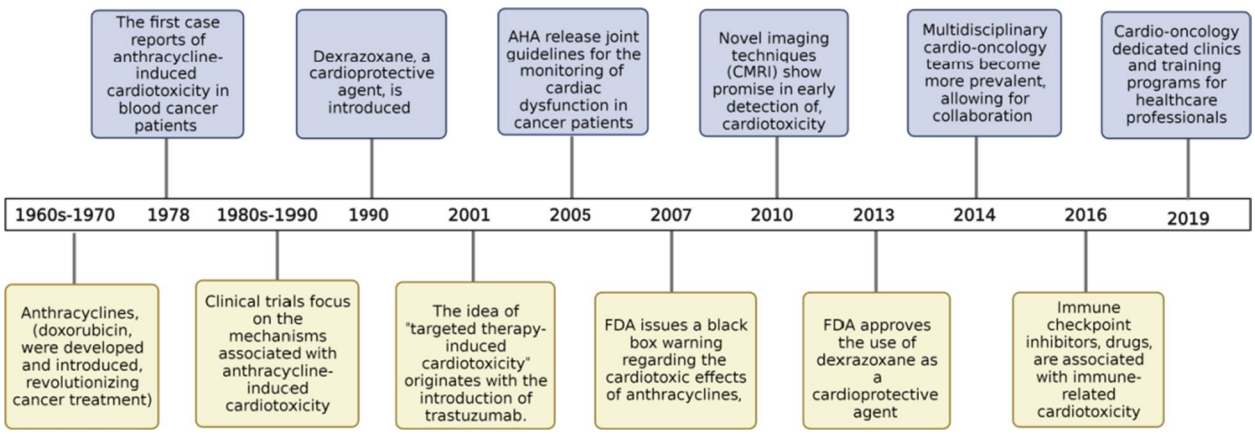

Fig. 1 A timeline history of cancer drug–induced cardiotoxicity.

arrhythmia, thromboembolism, ischemia, valvular heart disease, and sudden cardiac death. Cardiac complications such as arrhythmia and ischemia can occur acutely during cancer treatment, whereas heart failure and CRIC usually appear during years after completion of the treatment [4]. The type and severity of cardiovascular complications differ depending upon the actual cancer treatment. The risk of cardiovascular complications can be influenced by a number of factors, including patient's age, pre-existing cardiovascular disease, and the type and duration of therapy. As a result, it is critical for healthcare providers to monitor patients undergoing leukemia treatment for potential cardiovascular complications and to manage them promptly in order to reduce the risk of long-term cardiovascular damage [5].

Cardiotoxicity is a side effect of various cancer therapeutic targets. Chemotherapeutic drug anthracycline causes adverse cardiovascular sequelae in cancer patients. Cardiomyopathy and heart failure are the most common clinical manifestations of anthracycline cardiotoxicity [6]. When compared to non-anthracycline chemotherapy, treating with anthracycline-based chemotherapy increases the patient's risk of cardiotoxicity by 5 times [7]. In addition to anthracyclines, some chemotherapeutic agents such as alkylating agents, tyrosin kinase inhibitor (TKI), and Bruton's tyrosin kinase inhibitors (BTK) cause cardiotoxicity in patients with leukemia.

Troponin and brain natriuretic peptides serve as potential cardiac biomarkers for the early detection of cardiotoxicity in cancer patients undergoing chemotherapy or radiation therapy [4]. The prevention and management of adverse cardiovascular effects in blood cancer patients are a growing clinical issue. In the global context, decreasing the cancer therapy–induced cardiac manifestations in leukemia patients is a challenge for medical community, which recommend more evidence-based findings to overcome the manifestation and provide good therapeutic outcomes. The purpose of this review is to provide a clear picture of cardiovascular complications caused in leukemia patients as a result of various therapeutic strategies used during the treatment.

Risk factors for cancer therapy–related cardiovascular disease (CTRCD)

Risk factors related to cardiovascular diseases can be linked to patients or therapies, depending on the status of patient or therapy. Patient-related risk factors for cardiovascular disease include hypertension, diabetes, smoking, and age. It is worth noting that hypertension is associated with long-term cardiac hypertrophy and insufficiency [8]. Furthermore, genetic polymorphism seems to affect the individual response to chemotherapeutical drugs, increasing the cardiovascular disease. Blanco et al. show that patients with homozygous mutation in carbonyl reductase 3 (CBR3:GG) were more susceptible to cardiomyopathy risk after an exposure to low/moderate doses of chemotherapeutic drug anthracycline than subjects carrying wildtype genotypes (CBR3:GA/AA) [9]. In addition, presence of more cardiovascular peptides found in some cancer patients prior to chemotherapy has been linked to myocardial injury, which increased the risk of cardiovascular disease [10]. Other general and genetic conditions, such as female sex, black race, and Down syndrome in children, have been shown to predispose to cardiovascular injury in studies on pediatric subjects with leukemia or osteogenic sarcoma [11, 12].

The most common TRCD is caused by high-dose chemotherapy drugs, primarily anthracycline, biologic agents such as monoclonal antibodies, TKI, and radiation interventions. Several prediction models have been developed

to assess a risk of cardiovascular disease in patients treated with antineoplastic drugs [13–15]. This strategy aims to improve the individual clinical outcomes of chemotherapy-treated patients by reducing morbidity and mortality.

Chemotherapy drugs causing cardiotoxicity in blood cancer (Table 1)

Anthracyclines

Anthracyclines are class of drugs isolated from *Streptomyces* species. It is one of the most effective antineoplastic agents used to treat a wide range of hematological cancers and solid tumors [54]. Among them, doxorubicin, daunorubicin, and epirubicin have been shown to significantly improve clinical outcome in patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) [55, 56]. Doxorubicin is also used to treat non-Hodgkin's lymphoma, small cell lung cancer, and sarcoma, and now becoming the standard therapy for these malignancies [57]. The anticancer effect of anthracyclines derives from the inhibition of topoisomerase-II in tumor cells, which intercalate with DNA, disrupting the DNA double helix, preventing DNA and RNA synthesis, and promoting cell death [58].

Unfortunately, anthracyclines trigger adverse cardiovascular effects in cancer patients. Anthracycline-induced cardiac dysfunction (AICM) may be acute, sub-acute, and chronic, depending on the reversibility and onset of the toxicity. Acute toxicity affects less than 1% of global population, causing supraventricular arrhythmia, left ventricle (LF) dysfunction, and electrocardiogram (ECG) alterations. These injuries can eventually lead to chronic cardiotoxicity, which is usually irreversible. However, most of the cardiotoxic effects occur within 1 year of treatment, and result in at least 50% mortality [59]. According to Von Hoff et al., heart failure occurred in 2.2% of patients treated with 550 mg/m^2 of doxorubicin. Increased doxorubicin dosage increases the risk of congestive heart failure [59]. The authors thus confirmed the hypothesis that cumulative doses of doxorubicin increase the risk of cardiotoxicity. Other investigators showed that cumulative doxorubicin doses greater than 350 mg/m^2 could cause a dose-dependent decrease in left ventricular ejection fraction (LVEF), which was often asymptomatic and could be mitigated after drug discontinuation [60].

Several studies indicate that anthracyclines cause cardiotoxicity through a variety of mechanisms. Anthracycline-induced cardiac injury, in particular, begins with primary effects and progresses to intermediate and final effects [61]. Overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is one of the main mechanisms. Evidence suggests that ROS and RNS have important physiological functions at low concentrations because they act as secondary messengers in many signaling cascades in different cell types. Notably, ROS mediate the smooth muscle cells contractility and differentiation, vascular cells migration, and platelet activation in the cardiovascular system [62, 63]. Furthermore, ROS and RNS regulate epigenetic pathways such as DNA methylation and histone modifications [64]. Pathological states, such as cancer, increase of ROS levels, resulting in DNA

Table 1. Cardiotoxicity associated with various classes of cancer therapies

Class	Agents	Malignancies	Inhibitory mechanism	Targets	Cardiac manifestations	Management	Cardiotoxicity monitoring	References
Alkylating drugs	Ifosfamide	Sarcoma, lymphoma	-Cause endothelial dysfunction -Cause thrombosis -Direct DNA damage	-	HF/LVD/myopericarditis/arrhythmia			[16]
	Cisplatin	Lung, bladder, testicular, breast, esophageal, head and neck		-	Arrhythmia/ischemia VTE/HTN	-	-	[17]
	Cyclophosphamide	Breast, Leukemia, Multiple myeloma	-Alkylation of tumor DNA -Generate ROS	-	Cardiac tamponade/ arrhythmias/HF	-Cardiac tamponade-pericardiocentesis, dobutamine -Arrhythmias-antiarrhythmics -HF-D/C agent, ACEI, and β-blocker	-	[18]
	Bleomycin	Ovarian	-Through oxidative stress pathway -Inhibit nucleotide synthesis	-	Myocardial ischemia	-	-	[19]
	Melphalan	Multiple myeloma, leukemia, ovarian	-Inhibit nucleotide synthesis	-	Acute cardiomyopathy		-	[20]
Small-molecule TKIs and VEGF blocker	Lapatinib	Breast	-Inhibit angiogenesis -Cause endothelial dysfunction -Cause energy depletion -HF: abnormal mitochondrial biogenesis, increased apoptotic cell death, inhibition of AMPK and PDGFRs	HER2 (ERBB2) EGFR (ERBB1)	HF/LVD	-	-	[21]
	Ponatinib	Leukemia		Bcr-Abl, VEGFR, PDGFR, FGFR, Src, KIT, RET, FLT3	HF/LVD/HTN/ Ischemia ATE/VTE	-	-	[22, 23]
	Sorafenib	Renal cell carcinoma		Bcr-Abl, PDGFRa, c-KIT, VEGFRs, B-RAF, CSF-1R, PDGFRb, KIT, FLT3, RET, RET	HTN/HF/LVD/Ischemia	-HTN-ACEI and CCB -Thromboembolic Events-LMWH, edoxaban, or rivaroxaban -LV dysfunction-D/C agent, ACEI, and β-blocker	EKG, 2D- Echocardiography	[24, 25]
	Sunitinib	Renal, thyroid, sarcoma, gastrointestinal stromal tumor, pancreatic neuroendocrine tumor		VEGFR1/2/, c-KIT, PDGFRα/β, RET, CSF-1R, FLT3	HTN/HF/LVD/VTE/ ATE	-HF-D/C agent, ACEI, and β-blocker -HTN-ACEI and CCB -Thromboembolic Events-LMWH, edoxaban, or rivaroxaban	-	[26]

Table 1. (continued)

Class	Agents	Malignancies	Inhibitory mechanism	Targets	Cardiac manifestations	Management	Cardiotoxicity monitoring	References
	Nilotinib	Leukemia		ABL1/2, PDGFRα/β, c-KIT	Ischemia/VTE/ATE/QT prolongation atherosclerosis hyperglycemia/diabetes	-Thromboembolic Events-LMWH, edoxaban, or rivaroxaban -HTN-ACEI and CCB -HF-D/C agent, ACEI, and β-blocker -Arrhythmias-antiarrhythmics	-	[27]
	Ibrutinib	Lymphoma		BTK	Atrial fibrillation/HTN, bleeding/ventricular arrhythmia		-	[28]
	Regorafenib	Colorectal, hepatocellular, gastrointestinal		VEGFRs, B-RAF, KIT, RET, PDGFRa/b, FGFR1/2, Raf-1, CSF1R, DDR2, TrkA	HTN/myocardial ischemia	-HTN-ACEI and CCB -Myocardial ischemia-anticoagulation, aspirin, ADP receptor inhibitor	-	[29]
	Imatinib	Chronic myeloid leukemia	Inhibition of mitochondrial protection pathways	Bcr-Abl, PDGFRa, c-KIT	Thromboembolic events/HTN/HF	-Thromboembolic events-LMWH, edoxaban, or rivaroxaban -HTN-ACEI and CCB -HF-D/C agent, ACEI and β-blocker	-	[30]
	Dasatinib	Chronic myeloid leukemia	-	Bcr-Abl, PDGFRb, c-KIT, EPHA2, Src	Thromboembolic events/HTN/HF	-Thromboembolic events-LMWH, edoxaban, or rivaroxaban -HTN-ACEI and CCB -HF-D/C agent, ACEI and β-blocker	-	[31]
	Erlotinib	Non-small cell lung cancer, pancreatic cancer	-	-	Thromboembolic events/HTN	-Thromboembolic events-LMWH, edoxaban, or rivaroxaban -HTN-ACEI and CCB	-	[32••]
	Lapatinib	Breast	-	EGFR, HER2	HF/HTN/Arrhythmias	-HF-D/C agent, ACEI, and β-blocker -HTN-ACEI and CCB -Arrhythmias-antiarrhythmics	-	[33]
	Dabrafenib	Melanoma	-	B-RAF C-RAF, SIK1	Arrhythmia	-Arrhythmias-antiarrhythmics	-	[34]
	Trametinib		-	B-RAF, MEK1/2	HF	-HF-D/C agent, ACEI, and β-blocker	-	[35]
	Vemurafenib		-	B-RAF, C-RAF, A-RAF, ACK1	HF	-HF-D/C agent, ACEI, and β-blocker	-	[36]
Anti-metabolites	5-Fluorouracil	Colon, pancreatic, breast, head, and neck	-Inhibit angiogenesis -Cause endothelial dysfunction -Cause energy depletion -Generate ROS -Coronary vasospasm		Coronary vasospasm/ischemia/arrhythmia LVD/myocarditis		-	[37, 38]

Table 1. (continued)

Class	Agents	Malignancies	Inhibitory mechanism	Targets	Cardiac manifestations	Management	Cardiotoxicity monitoring	References
	Capecitabine	Breast, colon, gastric, pancreatic			coronary vasospasm/ischemia/arrhythmia/LVD		-	[39]
Anti-microtubule agents	Docetaxel	Breast, lungs	-Inhibit microtubule formation -Activate NCS-1 causing Ca^{2+} overload -Impaired cell division				-	[40, 41]
	Paclitaxel	Breast, ovarian, lung, sarcoma, bladder, cervical, gastric, esophageal, head, and neck					-	[42, 43]
	Vinblastine	Breast, colorectal, leukemia, lymphoma			Angina/MI	-Angina-aspirin, ADP receptor inhibitor, nitrate, β-blocker -MI-PCI or IV thrombolytics as per AHA guidelines	-	[44]
Protease inhibitors	Carfilzomib	Multiple myeloma	-Activation of caspase 3 -Inhibition of proteosome activity -Inhibit the chymotrypsin-like activity		HF/LVD/VTE, HTN ACS/pulmonary/HTN	-HF-D/C agent, ACEI, and β-blocker -Arrhythmias-antiarrhythmics -Cardiomyopathy-aspirin, statin, β-blocker -HTN-ACEI and CCB	-	[45•]
	Bortezomib				HF/arrhythmias/HTN/MI	-HF-D/C agent, ACEI, and β-blocker -Arrhythmias-antiarrhythmics -HTN-ACEI and CCB -MI-PCI or IV thrombolytics as per AHA guidelines	-	[46]
	Ixazomib				HF	-HF-D/C agent, ACEI, and β-blocker	-	[47]
Anthracyclines	Doxorubicin	Breast, sarcoma, lung, bladder, gastric, prostate, leukemia, lymphoma, others	Activate Necleus TopIIβ (inhibited by Dexrazoxane), -Generate ROS -Activate TopImt -Fe^{2+} overload -Damage transcription -Energy depletion -Prevent DNA synthesis -Apoptosis		HF/LVD/arrhythmia	Clinical assessment ECG Plasma biomarkers MUGA scan 2D- Echocardiography, Strain*, Biomarkers (troponin, BNP)	Clinical assessment ECG Plasma biomarkers MUGA scan 2D- Echocardiography, Strain*, Biomarkers (troponin, BNP)	[48]

Table 1. (continued)

Class	Agents	Malignancies	Inhibitory mechanism	Targets	Cardiac manifestations	Management	Cardiotoxicity monitoring	References
	Epirubicin	Breast, esophageal, gastric			HF/LVD/arrhythmia	-General-Dexrazoxane -LV dysfunction-D/C agent, ACEI, and β-blocker -HF-D/C agent, ACEI (enalapril), and β-blocker (Carvedilol) -Arrhythmias-antiarrhythmics	-	[49]
	Daunorubicin	Different leukemia			LV dysfunction/HF/ arrhythmias	-General-Dexrazoxane -LV dysfunction-D/C agent, ACEI, and β-blocker -HF-D/C agent, ACEI (enalapril), and β-blocker (Carvedilol) -Arrhythmias-antiarrhythmics	-	[50]
	Mitoxantrone	Prostate, breast			Arrhythmia/HF	-Arrhythmias-antiarrhythmics -HF-D/C agent, ACEI, and β-blocker	-	[51]
	Bleomycin	Lymphoma			Pericarditis/CAD/athero-sclerosis	-Pericarditis-NSAIDs, colchi-cine; prednisone if severe -CAD-statin, ADP receptor inhibitor, nitrate, β-blocker -Atherosclerosis-statins	-	[52]
	Mitomycin C	Bladder, anal, breast, head, and Neck			HF	-HF-D/C agent, ACEI, and β-blocker		[53••]

damage, reduced repair mechanisms, altered cell proliferation and survival, and genomic instability [62].

Anthracycline-based anticancer therapy causes an imbalance in ROS and RNS production, which modulates cellular and molecular pathways as well as the homeostasis of intermediate metabolic players (Fig. 2). These modulating mechanisms inevitably result in irreversible heart failure [65, 66]. ROS/RNS-induced cardiotoxicity is exacerbated in cardiovascular tissues because the hearth contains fewer antioxidant agents than other organs [67].

Further, the binding of anthracyclines and free intracellular iron exacerbates ROS effects [68]. As a result, maintaining the balance of ROS and RNS is crucial for preserving the function of cardiovascular system. Besides increased oxidative and nitrosative stress, another primary effect of anthracyclines is the inhibition of topoisomerase-IIB, which is highly expressed in many tissues, including the cardiomyocytes. Its enzymatic activity is known to be reduced by the treatment with doxorubicin, which form complex topoisomerase-IIB-doxorubicin causing altered DNA breakdown and repair mechanisms. Topoisomerase-IIB deficiency promotes DNA damage, activating p53 tumor-suppressor and causing mitochondrial injury. Topoisomerase-IIB inhibition, along with ROS and RNS, determines cardiomyocyte death [68]. Therefore, topoisomerase-II-B is a promising molecular target for preventing anthracycline-induced cardiotoxicity (AIC) [69].

Furthermore, anthracyclines cause cardiac dysfunction by releasing the high mobility group box 1 (HMGB1), a molecule that is primarily involved in the pathogenesis of arthritis and atherosclerosis [70]. As previously demonstrated [71], HMGB1 in cardiomyocytes combines with toll-like receptors

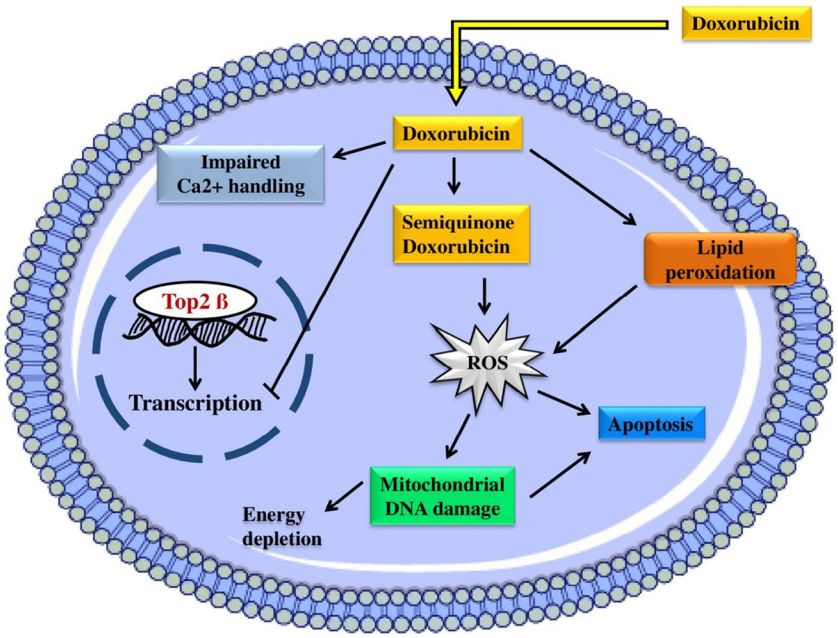

Fig. 2 Anthracycline (doxorubicin)–mediated inhibition of topoisomerase-IIB: molecular mechanism. Doxorubicin acts on Top2B, which causes genomic and mitochondrial DNA damage, leading to generation of ROS. Doxorubicin also leads to impaired Ca2+handling, and lipid peroxidation, resulting in overproduction of ROS and even cell death.

(TLR) 2 and 4, and triggers the overexpression of these receptors in heart failure patients [72]. In an experimental model, it was reported that the overexpression of TLR resulted in hypertension [68]. Indeed, TLR activation allows the release of inflammatory cytokines, such as TNF and IL-1, which significantly contributes to cardiac injury. As demonstrated in experimental studies on mice, the inhibition of TLR2 reduced cardiotoxicity by 13% and significantly reduced cardiac fibrosis and inflammation [71]. This evidence suggests that TLR2 may be a promising target for treat patients affected by cardiomyopathy or cardiotoxicity.

Anthracycline dosage and mode of administration, as well as their combination with other interventions, can all have a significant impact on cardiotoxic injury. According to the American Society of Clinical Oncology (ASCO), the cardiotoxic risk increases when patients are given high doses of anthracyclines (doxorubicin ≥ 250 mg/m^2 or epirubicin ≥ 600 mg/m^2), or when low doses of the same drugs are combined with radiation therapy. In addition, cardiac dysfunction can occur when anthracyclines are combined with other medications or when an additional risk factor, such as advanced age, is present [73]. When anthracyclines are administered as continuous infusion rather than a single bolus, the risk of adverse cardiac effects appears to be reduced. As previously shown, infusion of doxorubicin for 48–96 h reduces cardiotoxicity in adult patients by lowering the peak plasma levels [74]. This, however, causes cumulative drug effects, which may in turn compromise the rescue of already damaged cardiac cells. Furthermore, when applied to children with ALL, this alternative drug administration showed no benefit in improving cardiac function [75]. As a result, the replacement of single bolus of anthracycline with continuous infusion in cancer patients is still being debated.

According to the AIC, the main guidelines for the antineoplastic treatment in cancer patients recommend monitoring of LVEF, global longitudinal strain (GLS), and troponin levels before starting therapy, as these are the most commonly used clinical parameters for the evaluation of CTRCD. When LVEF and GLS levels are below physiological ranges, and troponin levels are elevated, cardiological counseling is strongly advised. In high-risk patients, an echocardiogram is also recommended 6 to 12 months after the therapy [76].

Alkylating agents

Alkylating agents are chemotherapeutic drugs that have been extensively studied in recent decades. They act as antineoplastic and immunosuppressant agents in a variety of blood cancers as well as lung cancer and sarcomas. Their antitumoral activity is based on protein downregulation caused by a change in DNA structure by the substitution of alkyl groups for hydrogen atoms. This event is particularly evident in rapidly dividing cells, such as cancer cells, which do not have time for DNA repair [77].

Cyclophosphamide is a widely used alkylating agent that works in combination with other drugs to treat leukemia [78], Burkitt's lymphoma [79], Hodgkin's [80] and non-Hodgkin's lymphoma [81], and multiple myeloma [82] besides lung [83] and breast cancer [84]. Cyclophosphamide-induced

cardiotoxicity (CIC) in humans is well known. When used at high dosage (> 150 mg/kg), myocarditis and fatal cardiotoxicity occur in more than 20% and 11% of adult subjects, respectively [85, 86]. The continuous infusion of 180 mg/kg cyclophosphamide over 4 days resulted in the following cardiac manifestations: reduction of left ventricular systolic function within 16 days from the treatment, ECG voltage alteration within 5 to 14 days from the therapy, heart failure in 28% of patients after 3 weeks from cyclophosphamide treatment. Surprisingly, the cyclophosphamide-related mortality rate has been estimated to be around 19% [85]. The incidence of cardiac adverse events was found to be in children than adults. This could be explained by a lower cyclophosphamide dosage in children due to their smaller size, or by an endogenous cyclophosphamide-resistance mechanism that protects the cardiovascular system from injury [87].

Apart from the dosage, other factors have been proposed to influence cardiotoxicity in cyclophosphamide treatment. Chest radiation and previous exposure to anthracyclines appear to be involved in the induction of cardiac dysfunction. According to Steinherz et al., patients who received 120–140 mg/kg cyclophosphamide for 1 week following previous administration of 100 mg/m^2 anthracyclines were at higher risk of cardiac dysfunction [88].

The mechanism underlying CIC is still not fully understood, and further investigations are needed. The histology and electronic microscopy images by Gottdiener et al. revealed vessel extravasation, tissue edema, and myocardial necrosis in patients with cyclophosphamide-associated lethal cardiotoxicity suggesting that endothelium damage is a critical factor for cardiac injury which may lead to the release of toxic metabolites, resulting in cardiomyocytes death and interstitial hemorrhage [85, 89].

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors represent the gold standard intervention in the treatment of several malignancies, most notably chronic myeloid leukemia (CML) [90, 91]. More than 30 TKI have been identified to date, and they are used in clinical practice due to their ability to inhibit several tyrosine kinases, such as BCR-ABL, KIT, EGFR, VEGFR, and PDGFR [92]. First TKI to be commercially available was imatinib (IM), a first-generation TKI, and it is still the drug of choice for treating CML. IM triggers BCR-ABL, responsible for CML in 90% of cases and ALL in 20% [93]. Because of IM, about 90% of patients had a high survival rate within 5 years of diagnosis. However, the onset of new mutations can be addressed as the responsible of resistance mechanisms in IM-treated patients. For this reason, second- and third-generation TKI have been developed for their stronger ability to inhibit BRC-ABL [94] and to trigger additional molecular targets, hence allowing a better clinical outcome [95]. Dasatinib and nilotinib, in particular, have been approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of newly diagnosed CML patients, IM-resistant patients, and pediatric patients [96].

Although TKIs are effective in improving the cancer patients management, their cardiotoxic effects are cause for concern. The inhibition of kinases like VEGFR, EGFR, PDGFR, and BCR-ABL affects the main pathways involved in cell proliferation, metabolism, and survival. Changes in molecular signaling, in particular, cause endothelial dysfunction, oxidative stress, increased apoptosis, altered protein synthesis, and decreased cell survival [97].

The most common clinical cardiovascular manifestations induced by TKI is undoubtedly hypertension. As shown in the work of Chu et al., sunitinib, a TKI approved by FDA for the therapy of renal cell carcinoma and gastrointestinal stromal tumor, induces significant hypertension in almost 50% of treated patients, and mitochondrial dysfunction as well as cardiomyocyte apoptosis in mice and cultured cardiac cells. The recovery of LV dysfunction and heart failure after drug discontinuation confirmed the sunitinib-induced cardiotoxicity [98].

Dasatinib, a second-generation TKI, has been associated to pulmonary arterial hypertension (PAH), in cancer patients [99]. Dasatinib was shown to induce endothelial cells alteration by reducing trans-endothelial resistance and increasing tight junction permeability, which could significantly contribute to the onset of hypertension in dasatinib-treated patients. Imatinib treatment, on the other hand, did not produce this kind of effect [100].

Despite an improvement of clinical features following dasatinib discontinuation in cancer patients, some subjects continued to exhibit symptoms and the cardiotoxicity for several months after drug discontinuation [99]. Moreover, according to Weatherald et al., PAH may remain in 37% of patients after dasatinib discontinuation, which suggest the importance of continuous follow-up in chronic diseases [101].

Besides dasatinib, other TKIs have been investigated as plausible causes of hypertension. Patients treated with lapatinib displayed PAH, as confirmed by normalization of blood pressure levels after lapatinib discontinuation [102]. Other studies suggested ponatinib [103] and nilotinib [104] as inductors of PAH, although these clinical studies rely on single subject evaluation. Studies indicate that TKI increase blood pressure by reducing nitric oxide production and damaging endothelial cells, resulting in increased vascular tone and higher vascular resistance, respectively [105, 106].

The onset of hypertension, as well as the patient population affected, can be highly variable. Sunitinib and sorafenib induce increased blood pressure in 15% to 47% of treated subjects, while the symptoms can occur after 24 h or within 1 year from the therapy [107, 108]. Other major clinical features of TKI-treated patients include heart failure and LV dysfunction. IM is well known to be cardiotoxic in humans. As shown previously, therapy with IM caused a significant reduction in LVEF after more than 7 months of treatment, which was associated with left ventricle dilatation. Electro-micrograph of heart biopsies highlighted abnormal myocytes structure, as well as mitochondrial alterations, cytosolic vacuoles, and glycogen accumulation in cardiomyocytes [109].

Experiments on IM-treated mice yielded results similar to those in humans, including mitochondrial dysfunctions and sarcoplasmic reticulum dilatation, resulting in LV dysfunction and dilatation [109]. The mechanisms underlying

TKI-related cardiotoxicity are typically classified as on-target and off-target toxicity. The on-target toxicity refers to a mechanism through which a molecule is specifically triggered. An example is given by the treatment with drugs acting against HER2 receptor. Because the HER 2 receptor plays a pivotal role in maintaining the proliferation and survival of cardiac cells, its inhibition results in LV dysfunction and cardiac injury [110]. On the contrary, the off-target toxicity involves the inhibition of kinases that are not primarily the pharmacological target, but cardiotoxicity may occur if these kinases play an important role in cardiovascular system. Kerkela et al. showed that 5′adenosine monophosphate–activated protein kinase (AMPK) activity, a key regulator of heart homeostasis, is limited by sunitinib treatment, resulting in cardiac dysfunction [111].

The European Society of Cardiology (ESC) listed the risk of recurrence of LV alteration based on the antineoplastic agents used for therapy [112]. Several TKIs, including nilotinib, ponatinib, sunitinib, and sorafenib, have been shown to promote acute coronary syndrome by inducing vasospasm, alteration of endothelial cells, and stimulating atherosclerotic events in coronary vessels [97]. Several TKIs, including nilotinib, ponatinib, sunitinib, and sorafenib, have been shown to promote acute coronary syndrome through vasospasm, endothelial cell alteration, and stimulation of atherosclerotic events in coronary vessels. QT prolongation is defined as a prolonged QT interval in ECG, which can result in severe cardiovascular dysfunction. This altered mechanism is associated with the usage of several therapeutic agents, including TKI. Kantarjian et al. indicated that different nilotinib concentrations induced QT interval prolongation up to 15 ms, promoting the lethal event of torsade de pointes [113].

Despite the fact that the exact mechanism is not fully elucidated, the most reasonable process explaining QT prolongation is the interference of antineoplastic drugs on ion channel cavity of human ether-a-go-go related gen (HERG), which is a member of the family of K + channels that regulates myocardial repolarization [114]. In alternative, TKI can cause an alteration in protein trafficking necessary for the proper location of HERG subunits in cell membrane [114]. TKI, on the other hand, can cause an alteration in protein trafficking, which is required for the proper positioning of HERG subunits in cell membrane [114]. Other mechanisms, such as drug interactions, myocardium heterogeneity, and genetic polymorphism, may be involved in QT prolongation. However, cancer patients can be predisposed for developing QT prolongation. According to one clinical study, 36% of subjects with advanced malignancies have baseline alterations, including atrial fibrillation and T wave abnormalities [115].

Bruton's tyrosin kinase inhibitors

Bruton's tyrosin kinase (BTK) inhibitors are novel targeted drugs approved for the primarily treatment of non-Hodgkin lymphomas (NHL), chronic lymphocytic leukemia (CLL), and mantle cell lymphoma (MCL) [116].

These antineoplastic agents function by triggering BTK, a member of the TEC kinase family that is fundamental for B-cell development, cell–cell adhesion, and cell survival [117]. Ibrutinib is one of the BTK inhibitors licensed in 2016 for the initial therapy of CLL, MCL, and Waldenström's macroglobulinemia (WM) [117]. This drug showed, in the RESONATE-2 phase 3 study, more

than an 80% lower risk of disease progression and death, allowing increased survival in CLL patients compared to previous antineoplastic agents [118].

Although it is a relatively new drug, its cardiotoxic activity is already well established. Indeed, hypertension and arrhythmia, as well as atrial fibrillation, represent serious concerns following ibrutinib treatment [119]. In particular, the incidence of atrial fibrillation in the population following more than 18 months of ibrutinib therapy is much higher than treatments with other antineoplastic agents used for the same cancer (16.6% versus 6.5%) [120]. Ibrutinib-related hypertension occurs in almost 80% of the treated population, and it may develop soon after the beginning of the therapy, thus requiring close surveillance of patients during antineoplastic treatment [121]. The proposed molecular mechanism for ibrutinib-related cardiac dysfunction is the alteration of TEC and PI3K-Akt pathways. Recent experiments on the human heart showed higher transcript levels of BTK and TEC in conditions of atrial fibrillation compared to sinus rhythm, demonstrating the importance of these pathways during cardiac stress [119].

PI3K-Akt signaling is a crucial pathway involved in the protection of heart during cardiac injury, able to prevent or delay cardiac disease progression [122]. Previous studies on transgenic mice with lower expression of cardiac PI3K-Akt activity highlighted an augmented risk of atrial fibrillation and evident atrial enlargement as well as cardiac fibrosis compared to normal mice. Similar results were obtained on humans, confirming PI3K-Akt as a pivotal pathway in cardiac protection [123].

As further demonstration, McMullen et al. showed a decreased activation of PI3K and Akt in rat ventricular myocytes when exposed to ibrutinib at concentrations of 0.1 to 1 M, respectively. Furthermore, Akt expression was inhibited by ibrutinib even after IGF1-induced PI3K stimulation [119].

The onset of ibrutinib-mediated ventricular arrhythmias appears as an uncommon consequence among the treated population [124•]. Indeed, a large retrospective multicentric study evidenced that the association between ibrutinib treatment and ventricular arrhythmia occurrence seems to be only around 0.5% [125]. However, this incidence should be monitored in future experiments. Recent studies correlate the onset of arrhythmias with the activation of Src kinases, a subfamily of protein tyrosine kinases expressed in different cell lines. Rutledge et al. showed that the inhibition of Src induced a diminished susceptibility to arrhythmia through the lesser internalization and degradation of connexin 43 in the heart walls [126]. More recently, Xiao and coworkers demonstrated in mice that c-terminal Src kinases represent the most probable molecular candidates leading to ibrutinib-induced arrhythmia [127].

Acalabrutinib (ACP) is a second-generation BTK used in treated subjects when ibrutinib resistance mechanisms occur. ACP was fast approved by FDA in 2017 for the therapy of MCL on the basis of promising results obtained in a phase 2 trial (ACE-LY-004) that showed an overall response rate of 80% in patients affected by MCL [128]. ACP was also tested for the management of CLL. Several preclinical experiments by Herman et al. demonstrated lowered tumor proliferation and raised survival in mice following ACP treatment [129, 130].To date, multiple trials are evaluating ACP effects on CLL patients with relapsed/refractory conditions both alone and in combination with other

drugs, showing encouraging results in terms of effectiveness and long-term safety [131–133]. According to recent clinical reports, ACP is well tolerated in treated patients and showed acceptable side effects, allowing 79% of patients to keep the antineoplastic therapy after a follow-up of 28 months [134].

Clinically significant adverse effects during ACP treatment were carefully monitored and among these the most frequent were neutropenia, headache, and, upper respiratory tract infections [131]. Based on phase 3 ELEVATE-TN trials, 5% of patients following ACP monotherapy showed cardiac arrhythmia HLGT, whereas 4% and less than 1% exhibited atrial fibrillation and supraventricular tachycardia, respectively. Similar effects were experienced when ACP was combined with obinutuzumab [132•]. Importantly, subjects suffering from hypertension and arrhythmia may develop higher risk of cardiac dysfunction after ACP therapy [135].

The recent phase 3 trial ELEVATE-RR compared the effects of ibrutinib with ACP in patients with relapsed CLL. This study showed a significantly reduced incidence of atrial fibrillation (AF) (9.4% versus 16%) and a higher survival rate when ACP was administered [133]. Among ACP-treated patients, 32% were 75 years old or older, while 40% and 60% had a history of AF and hypertension. In contrast to ibrutinib, AF events in ACP did not lead to drug discontinuation, and total cardiac events (24.1% versus 30%), as well as hypertension episodes (9.4% versus 23.2%), were less frequent [136].

These data collectively demonstrate that ACP has similar efficacy to the first-generation BTK inhibitor ibrutinib but exhibits a lower frequency of common adverse events, especially cardiovascular events, in relapsed or refractory CLL.

Zanubrutinib is another next-generation BTK-based drug developed to overcome the limitations exhibited by ibrutinib. As shown by Shadman et al. in a phase 2 study, zanubrutinib revealed greater specificity and stronger inhibitory activity compared to first-generation BTK inhibitors. In fact, zanubrutinib was able to inhibit 7 kinases in a profile evaluation of more than 300 kinases, while ibrutinib's action was directed against 17 kinases [137]. Moreover, zanubrutinib displayed better efficacy than ibrutinib in CLL and WM, likely due to the high plasma levels of the drug remaining in circulation, allowing its penetration into the bone marrow and lymph nodes [138••]. The higher bioavailability permits, in turn, an increased therapeutic exposure of zanubrutinib, and this seems crucial in achieving better efficacy than previous drugs. Furthermore, zanubrutinib holds improved pharmacokinetic properties, resulting in better drug-drug interactions, hence allowing its administration and tolerance in a major cohort of patients.

As of 2023, many countries have approved zanubrutinib for the treatment of MCL, MW, marginal zone lymphoma, CLL, and small lymphocytic lymphoma [138••]. Particularly, almost 4 thousand patients have been involved in 35 clinical studies across several world countries. The promising properties of zanubrutinib may be exploited in the future to explore new combinations of drugs that will help to obtain a synergistic therapeutic effect on blood malignancies, detailed in various classes of cardiotoxicity associated with different cancer therapeutics listed in Table 1.

Radiotherapy and cardiotoxicity

Radiotherapy is one of the most widely used conventional methods for cancer treatment, with approximately half of cancer patients undergoing this treatment. One author observed cardiac toxicity as a well-known side effect induced by radiotherapy, primarily affecting the thoracic region [139]. Radiation-induced heart injury is clinically crucial in subjects with Hodgkin's lymphoma and early-stage breast cancer, as these tumors require radiotherapy from a young age, leading to long-term heart complications [140].

Risk factors for radiotherapy-related heart injury include a dose higher than 30 Gy, exposure at a young age, a large volume of irradiated heart, a prolonged time of irradiation, and other comorbidities, such as hypertension, diabetes, and obesity.

A study on patients affected by Hodgkin's lymphoma demonstrated that subjects receiving a radiation dosage higher than 30 Gy had a 3.5 times greater risk of cardiac death compared to the normal population [141]. Although a dosage of 30 Gy seemed to be the threshold value to avoid serious cardiac impairment, more recent studies have highlighted the possibility of developing cardiotoxicity even at lower dose exposures in several cancers [142–144].

The modern technologies of radiotherapy, including intensity-modulated radiotherapy (IMRT), are more precise tools able to irradiate a specific anatomical region, avoiding the involvement of surrounding tissues. However, it is still debated if it is more convenient to concentrate the radiations in a narrow organ volume or to deliver a smaller dosage in a greater heart volume [145]. Besides this, other approaches to minimize cardiovascular side effects include avoiding overall irradiation [146] and the usage of protective drugs, including dexrazoxane [147].

In addition, the laterality of radiation delivery affects the clinical outcomes of patients. Indeed, a meta-analysis study by Cheng and colleagues demonstrated that subjects with breast cancer undergoing left-side radiotherapy exhibited a higher risk of cardiac death compared to participants treated on the right side [148].

As found by Galper et al. [149], and confirmed by Hancock [141] and Aleman [150], the risk of death following cardiac injury is strongly increased in younger individuals compared to the normal population. However, the risk of cardiac morbidity has been significantly related to old age, as the background risk of cardiac disease and the presence of other comorbidities can increase over time.

Radiation therapy did not show any significant relationship in promoting cardiac injury in males compared to females. In fact, male sex is an independent risk factor for cardiovascular events, suggesting that gender-wise associations may be involved with cardiotoxicity, which needs to be investigated in terms of molecular and biochemical aspects [151]. The pathophysiologic cascade of cardiac injury following radiation therapy is shown in the recent work of Koutroumpakis and colleagues [152].

Radiation therapy is known to induce cell senescence through DNA damage and oxidative stress [153]. Senescence, particularly that related to immune cells, causes a massive release of proinflammatory cytokines

such as TNFα, interleukin 6 (IL-6), and IL-1β [154]. These events, in turn, lead to a pro-thrombotic state following the overactivation of platelets and raised thrombin levels, as well as to metabolic impairments, including altered lipid metabolism and augmented glycolysis [152]. Arrhythmia, valve disease, myocardial fibrosis, and pericardial and coronary arterial disease represent the main complications following mediastinal irradiation in Hodgkin's lymphoma–treated patients [149]. The clinical manifestations observed during radiotherapy may arise even after 20 or 30 years from exposure, and the risk of dying is significantly increased if radiotherapy is in combination with anthracyclines at a dosage higher than 360 mg/m^2 [144]. Myrehuag et al. showed that patients treated with both mediastinal radiotherapy and doxorubicin displayed the highest rate ratio of cardiac injury compared to the normal population, confirming a strong association between radiation therapy and chemotherapy [155]. Pericardial diseases are the most frequent cardiac injuries consequent to the radiation therapy. They can appear as early or tardive manifestations, leading to acute pericarditis or effusions and constrictive pericarditis, respectively [156]. As shown by Heidenreich et al., asymptomatic Hodgkin's lymphoma patients receiving a total irradiation higher than 30 Gy showed a significant increase of pericardial wall thickness compared to control subjects [157]. This was accompanied by small pericardial effusions, which represent a serious risk for developing large effusions and further cardiac tamponade.

Arrhythmia is another frequent radiation-related therapy, as about three-fourth of survived Hodgkin's lymphoma patients receiving mediastinal radiation at a median dosage of 40 Gy showed abnormal electrocardiogram [158]. Supraventricular (63%) and ventricular (50%) premature complexes abnormalities as well as supraventricular (4%) and ventricular (4%) tachycardia were detected in survived pediatric patients affected by several blood cancers, including ALL, Hodgkin's lymphoma, and non-Hodgkin's lymphoma. The above-mentioned frequency percentages of these impairments, except supraventricular tachycardia, increased when radiation was coupled with anthracyclines [159].

Fibrosis is one of the main causes of cardiac disturbance, as it may impair electrical conduction mechanisms leading, in turn, to cardiac conduction delay, arrhythmias, and other dysfunctions [160].

Radiation-induced valvular disease is a clinical manifestation causing a typical increased thickness and calcification of mitral and aortic valves. The extent of valvular impairment is directly related to the latency period following radiation therapy. Hodgkin's lymphoma patients treated over 20 years with radiation therapy exhibited greater mitral (66% versus 28%) and aortic (61% versus 13%) thickening versus patients treated for 10 years. Furthermore, aortic and tricuspid regurgitation, and aortic stenosis were significantly higher compared to subjects irradiated for 10 years [157].

As shown in the work of Heidenreich, the aortic and mitral valve calcification was shown in 90% patients treated more than 20 years respect to 39% of subjects irradiated for 5 years [157].

Metabolic aspects in cardiotoxicity

Metabolic reprogramming is one of the key hallmarks of cancer and is emerging as a critical factor in the pathophysiology of heart failure [161]. In the heart, cardiac cells adapt to different types of biological stress, including oxygen, nutrient, and hydrodynamic environment, by accelerating nutritional uptake followed by metabolic adaptation [162, 163]. Metabolic rewiring promotes structural remodeling by facilitating the expression of specific genes and biosynthesis of proteins leading to support rapid growth [164, 165]. All these events allow cardiac contraction and cell survival. In respect to cancer, the heart is always susceptible to a unique combination of challenges defined by tumor heterogeneity and potentially cardiotoxic exposures.

The main metabolic constituents of the heart are fatty acids (60–90%) and carbohydrates (10–40%). A significant pool of ATP (95%) in the heart is generated through mitochondrial fatty acid β-oxidation (FAO) followed by glycolysis to meet cardiac metabolic demand [166]. The increase in glycolysis and up-coupling to glucose oxidation via fermentation leads to increased production of lactate and protons (H+) in the cytoplasm. This accumulation of H+ ions results in a decline in cardiac efficiency since cardiomyocytes use a bulk amount of ATP to restore iron homeostasis, at the expense of ATP-dependent contractility. Thus, this transition in energy metabolism hampers cardiac contractility and conductance [167].

Recently, several metabolic pathways have been distinguished in the failing myocardium. Therefore, the emergence of metabolic therapies might be beneficial against several forms of heart failure in both animals and patients [168]. In the heart, the myocardium, the most energetically demanding organ, predominantly utilizes long-chain fatty acids and glucose as the primary nutritional substrates to generate ATP required for myocardial contractility [167]. Hypoxia-inducible factor 1 α (HIF1α) is induced in the failing myocardium and is linked with the increased expression of glucose transporters, glycolytic enzymes, and pyruvate dehydrogenase kinase (PDK) [169]. Thus, HIF1α can directly increase glycolysis and inhibit glucose oxidation through the induction of PDK, leading to a decrease in cardiac functioning. Several studies have demonstrated that coupling glycolysis with glucose oxidation can improve cardiac efficiency in several heart failure conditions. For example, several chemotherapeutic agents, including anthracyclines or tyrosine kinase inhibitors, are associated with cardiac metabolic dysfunction [170–172]. These clues are providing further ideas that metabolic therapies could be beneficial against a variety of cardiotoxic chemotherapy agents.

In the current scenario, cancer therapy–induced cardiotoxicity is a major concern for both cancer and heart patients. Several potential factors, including cancer therapy, exposure of patients to various chemo drugs, and host and environmental factors, may contribute to the prevalence of cardiotoxicity. The metabolic views of cardiac manifestations, including cardiotoxicity, are growing exponentially. These inevitable side effects arise from the extensive use of anticancer and chemotherapeutic drugs. Chemotherapy, the standard treatment method consisting of several cytotoxic agents used in leukemia,

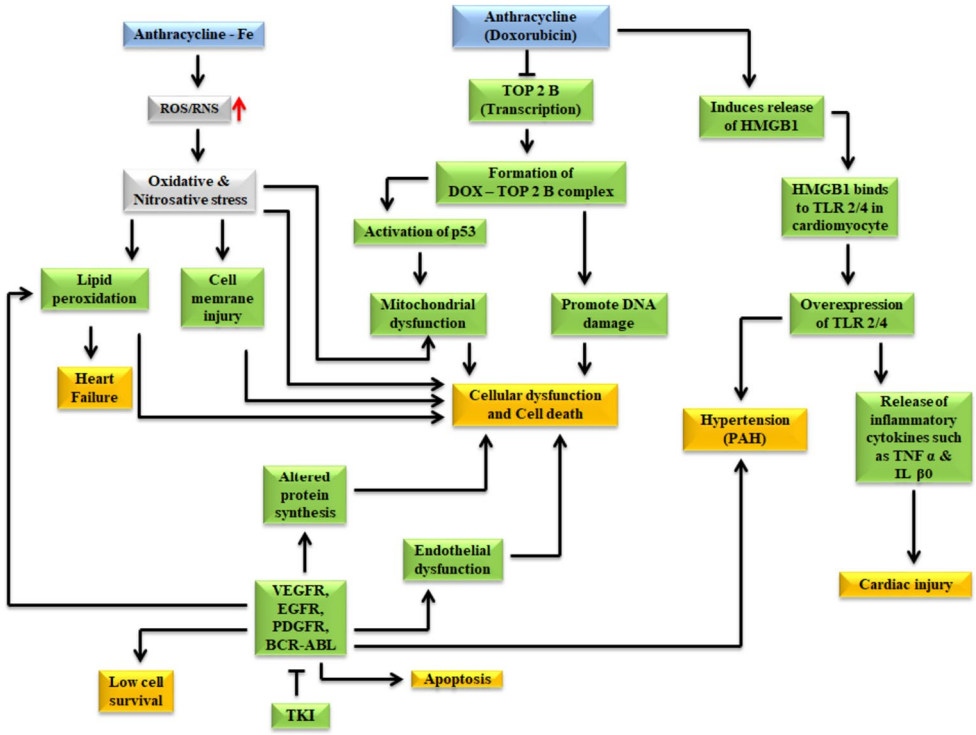

Fig. 3 Schematic representation of metabolic changes in cardiomyocytes during the pathogenesis of cardiotoxicity induced by chemotherapeutic drugs. TOP 2 B, which have high expressivity in normal cells, gets inhibited by anthracyclines, such as DOX. The formation of DOX-TOP 2 B complex promotes the mitochondrial as well as DNA damage, which eventually leads to cellular dysfunction and cardiomyocyte death. When anthracycline gets combined with iron, it increases ROS and RNS concentration, leading to oxidative and nitrosative stress. This stress condition causes lipid peroxidation, cell membrane injuries, and even heart failure and cardiomyocyte death. DOX induces release of HMGB1, which binds with TLR 2/4 on cardiomyocyte, making it over expressive. It leads to hypertension, causes release of cytokines and eventually cardiac injury. Similarly, TKI inhibits VEGFR, EGFR, PDGFR, and BCR-ABL, causing altered protein synthesis, endothelial dysfunction, low cell survival, lipid peroxidation, and ultimately cell death. DOX, Doxorubicin; TOP2B, Topoisomerase-2B; ROS, reactive oxygen species; RNS, reactive nitrogen species; HMGB1, high mobility group box 1; PAH, pulmonary arterial hypertension; TLR 2/4, toll-like receptor 2/4; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor.

shows an increased efficiency of up to 85% in inducing remission [173]. In recent trends, the use of combination therapy has been recommended, resulting in synergistic side effects and still existing as a main cause of treatment failure and drug development abrogation [174]. The association between metabolic remodeling and cardiotoxicity has been correlated with different cancer therapy such as nilotinib in chronic myelogenous leukemia [175, 176], copanlisib in relapsed follicular lymphoma [177], all the classes of anticancer drugs used in the treatment of pediatric leukemia, anthracyclines are most known for their toxic effects on cardiac tissue [178], copanlisib in relapsed follicular lymphoma, and androgen deprivation (AD) in prostate cancer. Of all the classes of anticancer drugs used in the treatment of pediatric leukemia, AD is most known for their toxic effects on cardiac tissue. These were found to be involved in dysregulated glucose and hyperglycemia

or hypercholesterolemia. AD is a classical anticancer drug act at the nuclear level by DNA intercalation, topoisomerase 2β (TOP2β) inhibition, and production of reactive oxygen species (ROS), that eventually triggering the cellular apoptosis pathways [179]. Imatinib's potent inhibition has inspired the treatment of these diseases, but concerns have been gaining more attention about cardiotoxicity linked with its usage [180]. A loss or alteration of cardiac metabolic pathways can be observed in ischemic heart failure, and remodeling of cardiac metabolism likely plays a role in the pathophysiology of cancer therapy–induced cardiotoxicity (CTIC) [181, 1823.

Immune checkpoint inhibitors and cardiotoxicity

Immune checkpoints refer to inhibitory pathways that are essential for maintaining self-tolerance and reprogramming immune responses. Tumor cells adapt to follow the same inhibitory pathways to avoid immune detection and destruction [183].

In the last few decades, immune checkpoint inhibitors (ICIs) have emerged as a backbone of systematic treatment for many types of cancer, including leukemia. Tumor cells exhibit different phenotypes that express neoantigens and mutated genes/proteins, which immune cells can attack as foreign entities and destroy. However, many cancer cells display oncologic factors that inhibit immune efficiency, allowing them to grow exponentially. Over the past few years, the development of immunotherapeutic regimens in oncology has revolutionized the clinical management of advanced-stage carcinoma with a dismal prognosis [184].

The revolution in cancer immunotherapy comes with the development of ICIs, which are monoclonal antibodies targeting host immune negative regulator receptors, including programmed cell death receptor 1 (PD-1) and programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4). These receptors downregulate the immune response by decreasing T-cell proliferation and migration or by increasing Treg cells. Tumor cells have been adapted by modulating the expression of these ligands to evade the local immune response and promote proliferation [185, 186]. The first ICI approved by the FDA for metastatic cancer was ipilimumab, a CTLA-4 antagonist [187]. Later, several ICIs were approved, such as monoclonal antibodies against PD-1, like nivolumab or pembrolizumab; ligands of PD-L1, such as atezolizumab; and CTLA-4, such as ipilimumab. In addition, monoclonal antibodies against PD-L1 have shown unprecedented success in a broad range of solid tumors [188–190], as well as hematological malignancies [191, 192]. They all have a synergistic effect and can also be used in combination.

However, PD-1 and PD-L1 can also be expressed in rodent and human cardiomyocytes [193]. Several animal studies have shown that CTLA-4 and PD-1 deletion can cause autoimmune myocarditis [194]. Interestingly, previous data have demonstrated that cases of myocarditis and fatal heart failure have been frequently reported in patients with cancer treated with immune checkpoint inhibitors (ICIs) [195]. The mechanism of ICI-related cardiac

toxicity is not yet fully revealed. Histological clinical profiling of patients and monkey models with ICI-associated myocarditis has indicated that the infiltration of predominant CD4 + /CD8 + T lymphocytes and a few macrophages (CD68 + cells) is the crucial cause of ICI-associated myocarditis [196, 197]. ICIs are specialized in blocking inhibitory signals from tumor cells to T cells that track, recognise, and destroy malignant tumors [198]. Cardiac toxicity due to ICIs is a rare event, with an incidence of up to 1%, but it is often brutal and can be life threatening. Most common cardiac manifestations seen in patients are cardiac fibrosis, cardiac arrest, autoimmune myocarditis, cardiomyopathy, heart failure (HF), pericardial involvement, and vasculitis [193, 199]. Among them, the development of fulminant myocarditis, a potentially fatal condition which has been the primary focus for the cardio-oncology researchers [193]. Cardiotoxicity may be reversible or irreversible and can occur after several months or years of treatment [200]. The extensive uses of ICIs from the past few years have been evidenced for numerous cardiovascular toxicities and cardiac dysfunction. In addition, cytotoxic agents such as anthracyclines appear as a most relevant problem associated with cardiotoxicity. However, various targeted therapies and chemotherapeutic options affect signaling pathways that can also induce cardiotoxicity [201].

Biomarkers of cardiac dysfunction

Echocardiogram is referred to as the gold standard approach to diagnose cardiac dysfunctions leading to ventricular alterations, as confirmed by the European Society of Cardiology in 2016 [112]. However, in many cases, the diagnosis is made too late, when the decline in EF has already occurred. Therefore, the early detection of cardiotoxicity during chemotherapy or radiation therapy represents a crucial point in managing patient outcomes.

Biomarkers are measurable biological variables that serve as indicators of normal or pathogenic biological processes or pharmacologic responses to a therapeutic intervention. An ideal biomarker must have the ability to diagnose a particular disease condition with high sensitivity, specificity, reproducibility, and low costs. The two most accepted cardiac biomarkers for acute coronary syndrome and heart failure are troponin and brain natriuretic peptides (BNP), respectively [4].

Troponin, particularly types I (TnI) and T (TnT), is the biomarker of choice to detect cardiac injury [202]. In fact, increased levels of this marker are predictive of reduced ventricular function and are associated with severe cardiac output. As shown by Cardinale et al., the levels of troponin increase proportionally to the cycles of chemotherapy with anthracyclines, confirming the strong correlation between the risk of cardiac dysfunction and this class of drugs [203]. Troponin allows the recognition of even a small number of cardiac cells, making the treatment fast and avoiding irreversible cardiac dysfunctions [204].

Ventricles release and its inactive N-terminal amino acid fragment NT-proBNP in response to volume overload and/or wall stress [205]. In order to

maintain euvolemia, BNP induces natriuresis and diuresis [4]. Currently, it is recommended to measure natriuretic peptide levels in patients with heart failure because it provides valuable diagnostic, therapeutic, and prognostic information [206]. Apart from troponin, natriuretic peptides are also the most commonly researched biomarkers in the context of CRIC (cancer radiation–induced cardiotoxicity). According to several studies, they are more sensitive biomarkers of cardiotoxicity than echocardiography. According to a study, after the completion of chemotherapy, NT-proBNP was significantly elevated at multiple moments, while there was no significant change in LVEF (left ventricular ejection fraction) [207]. High-sensitivity C-reactive protein, IL6, fatty acid–binding protein, and neuregulin-1 show independent correlation with a greater decline in LVEF with exposure to anthracyclines [208, 209].

Prevention of cancer therapy–related cardiac dysfunction

Dexrazoxan

The only FDA-approved cardioprotective agent for anthracycline-induced cardiotoxicity is dexrazoxane; it is a very efficient cardioprotective remedy against anthracyclines in different cancer types in both adults and children [210]. The ability of dexrazoxane to chelate iron was previously thought to be the primary mechanism of cardioprotection [211]. Lyu et al. revealed that dexrazoxane changes Top2's configuration to a closed-clamp form through tight binding to Top2's ATP-binding sites, thus preventing anthracyclines from binding to the Top2 complex [212]. Lipshultz et al. demonstrated the protective effect of dexrazoxane on cardiac function, particularly of LV structure and function, with no adverse effect on relapse risk, secondary malignancy frequency, or survival in a controlled random trial of 205 children [213].

Beta-Blocker, ACE inhibitors, or ARBs

Beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin-receptor blocker (ARBs) have been tested in randomized controlled trials for the prevention of anthracycline-induced (AC-induced) cardiotoxicity [211]. Beta-blockers have great role in the prevention of AC-induced cardiotoxicity, due to their important cardioprotective action. Carvedilol is a beta-blocker drug, dosage, and optimal administration timeline in cancer patients that still remains unclear [214]. LVEF (left ventricle ejection fraction) dropped significantly after chemotherapy in placebo or control groups, but not in intervention groups. Doxorubicin administration as a continuous infusion to lower peak blood concentrations has also been evaluated to prevent anthracycline-induced toxicity in children and adolescents [215].

Conclusion

The extensive use of several established and more potent or even newer therapeutic agents has improved the health condition of cancer patients. Besides, many of these cancer therapies are associated with cardiotoxicity, which is now a significant challenge for both oncologists and cardiologists. Cardiotoxicity in cancer patients undergoing treatment is a serious concern, particularly for those with blood cancer. While these drugs can effectively target cancer cells, they can also damage the heart and cardiovascular system, leading to potentially life-threatening complications. Our better understanding of the cellular, biochemical, and genomic mechanisms of cardiotoxicity enables us to detect the susceptibility of patients to cardiotoxicity before starting cancer treatment. It is important for healthcare providers to closely monitor patients undergoing cancer treatment, especially those at higher risk for cardiotoxicity, such as those with pre-existing heart conditions or a history of certain types of cancer. Early detection and intervention can help prevent or minimize the extent of cardiotoxicity.

Many studies have shown that dexrazoxane can prevent anthracycline-induced cardiotoxicity in both children and adults. Therefore, the use of dexrazoxane must be taken into account for patients treated with anthracyclines. Research into novel treatments and approaches to reduce the risk of cardiotoxicity is ongoing. These include the use of newer targeted therapies and imaging techniques to detect early signs of cardiac damage. In addition, lifestyle modifications such as exercise and a heart-healthy diet may also help reduce the risk of cardiotoxicity in cancer patients. Ultimately, the goal is to strike a balance between effective cancer treatment and minimizing the risk of cardiotoxicity to improve outcomes and the quality of life for blood cancer patients. Therefore, careful selection of chemotherapy agents, monitoring of cardiac function, and the use of cardio-protective agents can help mitigate the risk of cardiotoxicity.

Declarations

Author contribution

The author HKV has conceived the study. VC, EA, RA, and YKR have retrieved the data. VC, EA, YKR, RA, LVKS B, and HKV wrote the manuscript and approved the final version and made manuscript technically sound.

Compliance with Ethical Standards

Conflicts of Interest
The authors declare no competing interests.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Ethics Approval and Consent to Participate
Not applicable.

Consent for Publication
All the authors have read the manuscript and have approved this submission.

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- • Of importance
- •• Of major importance

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