CHEMOTHERAPY-INDUCED CARDIOTOXICITY

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Abstract

Cardiotoxicity is one of the most important side effects of first-line chemotherapy medications. It is influenced by genetic variation, whereby the relationship between the chemotherapeutic dose and the risk of cardiotoxicity can be altered. The incidence of cardiotoxicity depends on the substance used in the therapeutic modality of cancer and can reach an incidence of 30% during a three-year follow-up. The main element of the clinical picture is systolic dysfunction of the left ventricle, with symptoms of heart failure, which can change or stop oncological therapy, along with pharmacological treatment of heart failure. These symptoms can occur during prolonged use of cancer therapies, monitoring the patient is advisable. Considering the increasing success of oncology therapy and the extension of life, as well as the improvement of the quality of life, a multidisciplinary approach, as well as the symbiosis of the work of cardiologists and oncologists, is imperative. Patient stratification concerning oncological treatment modality is imposed as part of a cardiologist's daily work from the beginning of cancer treatment.

Keywords: cardiotoxicity, chemotherapy, treatment, prognosis

Introduction

Cardiotoxicity is one of the most important side effects of first-line chemotherapy medications, which can result in a poor prognosis and a lower survival rate[1]. Cytotoxic agents can often directly or indirectly induce cardiovascular injury through various mechanisms, increasing the risk of cardiovascular disease[1]. Age, obesity, *diabetes mellitus*, and the underlying heart conditions hypertension, coronary artery disease, structural heart disease, and cardiomyopathy are risk factors for chemotherapy-induced cardiotoxicity[2, 3]. Additionally, existing cardiovascular diseases and conditions, namely left ventricular ejection fraction < 50% or symptomatic heart failure, coronary disease, left ventricular hypertrophy, cardiomyopathies, arrhythmias (both supraventricular and ventricular rhythm disorders), classic cardiovascular risks, family history of early cardiovascular disease, arterial hypertension, *diabetes mellitus*, dyslipidemia, smoking, alcoholism, lack of physical activity, also play a role in the development of cardiotoxicity induced by such agents[4]. Meanwhile, oncological cardiovascular risks include old age, chemotherapy in childhood, trastuzumab use in people over 50 years old, anthracycline use in people over 65 years old, previous use of anthracyclines, cumulative dose of anthracycline, combined chemotherapy, and prior mediastinal or chest therapy[4]. A further possible risk factor for the cardiotoxicity of cytotoxic agents is the concurrent administration of other medications exhibiting cardiac adverse effects[5]. Chemotherapy-related cardiotoxicity is also influenced by genetic variation, whereby the relationship between the chemotherapeutic dose and the risk of cardiotoxicity can be altered[6, 7]. Clinical manifestations of cardiotoxicity related to cytotoxic agents range from arrhythmias or a decline in cardiac function to sudden death[8]. Furthermore, a constant risk factor for cardiotoxicity is cumulative chemotherapeutic exposure. The limit value of the cumulative anthracycline dose, which represents the limit of extremely high risk for the manifestation of complications, has yet to be precisely defined. In 2012, the critical cumulative dose of doxorubicin was 500 mg/m^2; in 2016, it was 250 mg/m^2, while the American Society of Clinical Oncology recommends 250 mg/m^2 (there are also described cases of severe cardiotoxicity at lower doses)[4].

It is well-recognized that common chemotherapy medications like anthracyclines display toxic effects on the cardiac muscle[9]. Following anthracyclines, fluoropyrimidines are considered the second most common cytotoxic agents resulting in cardiotoxic effects, though rare but potentially fatal side effects, with an incidence of up to 30%[9]. Additionally,

immune checkpoint inhibitors (ICIs), as well as molecularly targeted antiangiogenic medications, including vascular endothelial growth factor (VEGF) inhibitors and tyrosine kinase inhibitors (TKIs), are available for the treatment of cancer; the cardiovascular effects of the later ones may start early and not be dose-dependent, while some can be significant and potentially fatal[10, 11]. Also, the human epidermal growth factor receptor 2 (HER2) trastuzumab has demonstrated a low to moderate risk of cardiotoxicity, as well as biologic response modifiers, topoisomerase inhibitors, alkylating agents, microtubule-targeting drugs, antimetabolites, antitumor antibiotics, monoclonal antibodies, among others[12, 13]. The prognosis of cancer patients is improved by cytotoxic drug-induced cardiotoxicity[9, 14]. The definitions regarding cancer therapy-related cardiac dysfunction (CTRCD) range from mild to severe, whereby symptomatic CTRCD referring to heart failure (HF) demands inotropic support, mechanical circulatory support, or consideration of transplantation, while asymptomatic CTRCD, when severe, is defined as a new left ventricular ejection fraction (LVEF) reduction to < 40%[4]. Thus far, cut-off values for cardiac biomarkers, such as natriuretic peptides (NP) and cardiac troponin (cTn) in patients receiving cytotoxic therapies have not been clearly defined, and it is essential to take into consideration age, sex, renal function, underlying atrial fibrillation or pulmonary embolism, obesity, and infections as factors that may alter their levels in these patients[4]. Not only are cardiac biomarkers useful for CTRCD screening and diagnosis, but they also play a role in guiding therapy, as their release varies in different cancer treatments depending on the timing of treatment initiation and comorbidities[4]. This article aims to provide an overview of cardiotoxic effects associated with different groups of cytotoxic agents, the mechanisms involved, as well as their treatment.

Occurrence and the mechanism of cardiotoxicity

The occurrence of cardiotoxicity, the mechanism of cardiotoxicity, the cumulative dose concerning the pharmacological agent, as well as the treatment, are displayed in table 1.

Clinical presentation of chemotherapeutic toxicity

Cardiotoxicity of chemotherapy can manifest itself through different clinical presentations: heart failure, myocarditis, pericarditis, arrhythmias, hypertension, ischemia and myocardial infarction, and various thromboembolic incidents.

Heart failure

Transient or permanent decline in left ventricular (LV) function is a manifestation of chemotherapeutic toxicity[14, 15]. Anthracycline-induced LV systolic dysfunction brought on as fatigue, dyspnea, orthopnea, edema, and cardiogenic shock in cancer survivors are comparable to those seen in individuals with other causes of heart failure and is linked to a significant early increase in serum troponin in 30-35% of anthracycline-treated patients[15, 16]. In addition, patients may exhibit arrhythmias triggered by elevated filling pressures[15]. Cardiotoxic effects of the anthracyclines are dose-dependent, and they are more common with mitoxantrone and idarubicin than with doxorubicin; these rates are fundamental concerning the recommended cumulative lifetime doses, which should not be exceeded to prevent clinically significant cardiotoxicity (table 1)[16]. Furthermore, anthracycline chemotherapy should typically be avoided in patients with an LVEF ≤ 40%; instead, other non-anthracycline-containing regimens should be considered. Before starting anthracycline-based chemotherapy, an LVEF assessment is performed to detect any preexisting LV dysfunction[15-17]. For the primary prevention of anthracycline-related cardiotoxicity, dexrazoxane is an effective medication, which exerts its action by chelating intracellular iron, thereby preventing the generation of iron-assisted oxidative radicals and inhibiting topoisomerase II-beta (an enzyme linked to anthracycline cardiotoxicity)[17]. Posttreatment monitoring is based on the differences in the ideal measurement of LV function, the threshold for testing, and the interval for testing[15, 17]. Additionally, echocardiographic assessment is performed throughout the treatment after each cycle of chemotherapy as well as annually after its completion in patients with acute cardiotoxicity who will undergo further anthracycline exposure or in those with preexisting LV dysfunction[17]. The survival rates of patients with clinical HF triggered by anthracycline toxicity are comparable to those of individuals with HF caused by other factors[15-17]. Dysfunction of the left ventricle has also been observed in patients treated with specific VEGFR tyrosine kinase inhibitors (axitinib, lenvatinib, pazopanib, ripretinib, sunitinib, and sorafenib) (table 2)[18, 19].

Cardiotoxicity of the HER2-targeted drug trastuzumab manifests as a reduction in left ventricular ejection fraction, but this effect can be reduced by discontinuing the treatment (table 1)[12]. In patients with LVEF of 40-50%, age > 50 years, and hypertension, the risk of heart failure is slightly increased when trastuzumab is administered after anthracycline therapy[12, 16]. Moreover, lapatinib, an orally active tyrosine kinase inhibitor affecting both HER2 and the EGFR, has a more favorable cardiotoxicity profile than trastuzumab, according to preliminary results from clinical studies, while beneficial effects on left ventricular ejection fraction (with the recovery of LVEF up to a value of ≥ 50%) were also reported in 87% of patients on pertuzumab, a monoclonal antibody binding to a different epitome of HER2[20, 21]. Dilated cardiomyopathy can coexist with immune-checkpoint inhibitor-related impairment of left ventricular function[22]. In addition, cardiac adverse events, especially new-onset HF, as well as coexistent cardiovascular comorbidities and an increased baseline CV risk, have been demonstrated to occur

Table 1. Cytotoxic agents inducing cardiotoxicity[9-15]

GROUP	CYTOTOXIC AGENTS	INDICATIONS	CARDIOTOXIC EFFECT	MECHANISM OF CARDIAC TOXICITY	RELATED TO CUMULATIVE DOSE	TREATMENT OF CARDIAC COMPLICATIONS
Anthracycline	Doxorubicin Daunorubicin Idarubicin Epirubicin Mitoxantrone	Hodgkin lymphoma, non-Hodgkin's lymphomas, acute leukemia	HF, arrhythmias	Oxidative stress, topoisomerase-II mediated cell death, the time course of cardiotoxicity (with early ↑ in cardiac troponin, ↓ in LVEF)	Yes (with doxorubicin)	Limit the cumulative dose, administering the medication via infusion rather than bolus dose, liposomal formulations
Immune checkpoint inhibitors	PD-1 inhibitors - nivolumab, pembrolizumab, cemiplimab, dostarlimab PD-L1 inhibitors - atezolizumab, avelumab, durvalumab CTLA-4 inhibitors - ipilimumab, tremelimumab	Hodgkin lymphoma, various types of cancer	Myocarditis, pericarditis, HF, arrhythmias, vasculitis	Target cytotoxic T lymphocyte-associated antigen 4, programmed cell death receptor 1, and programmed cell death ligand 1	No	High-dose steroids; if no response, (methylprednisolone 1 g every day and either mycophenolate, infliximab, or anti-thymocyte globulin) If elevated troponin levels or conduction abnormalities occur: immediate transfer to the coronary care unit or cardiac transplant Life-threatening cases: abatacept or alemtuzumab
Fluoropyrimidines	Fluorouracil Capecitabine	Head and neck, esophagus, stomach, colon, rectum, anus, and breast malignancies	Myocardial ischemia	Coronary vasospasm, a direct myocardial toxic effect due to the antimetabolite effects	No	If symptomatic: discontinue therapy
Antiangiogenic agents	Bevacizumab Ramucirumab Aflibercept VEGFR tyrosine kinase inhibitors - sunitinib, sorafenib, pazopanib, vandetanib, cabozantinib, axitinib, ponatinib, lenvatinib, regorafenib, tivozanib	Metastatic non-squamous non-small cell lung cancer, renal cell carcinoma, ovarian cancer, cervical cancer, glioblastoma multiforme	Hypertension, thromboembolic disease, left ventricular dysfunction, myocardial ischemia, prolongation of the QTc interval, thrombotic microangiopathy	Vasoconstriction mediated by endothelins, with reduced myocardial perfusion, disruption of endothelial cell homeostasis by a dose-dependent increase in mitochondrial superoxide generation and reduced nitric oxide availability myocyte necrosis, decreased cardiac repair, targeting the PDGFR resulting in coronary microvascular dysfunction, systemic capillary rarefaction leading to afterload	When combined with doxorubicin	If pericarditis: corticosteroid therapy
Microtubule-targeting drugs	Vinca alkaloids - vinblastine, vincristine, vinorelbine Taxanes - paxlitaxel, nabpaxlitaxel docetaxel Eribulin mesylate Ixabepilone	Acute lymphoblastic leukemia, Hodgkin lymphoma, non-Hodgkin's lymphomas, ovarian cancer, breast cancer	Hypertension, myocardial ischemia, infarction, AV conduction block, VT, bradycardia	Angina, decrease in ejection fraction, conduction abnormalities, cardiovascular collapse	When combined with doxorubicin	If impaired cardiac function during therapy or cardiac ischemia: discontinue therapy
Antimetabolites	Fludarabine Pentostatin Cladribine Methotrexate Cytarabine	Hematologic malignancies, bone marrow transplantation agent	Ischemia, HF, syncope, MI, SVT, VT, pericarditis, pericardial effusion, cardiac tamponade	Purine antagonist disrupt the normal metabolic processes of cardiomyocytes, leading to hypotension and chest pain	Yes	If symptoms are severe: close monitoring and supportive care (oxygen therapy), temporarily withhold or reduce the dosage
Alkylating agents	Cyclophosphamide Ifosfamide Cisplatin Busulfan Trabectedin	Lymphomas, leukemia, autologous hematopoietic stem cell transplantation, allogeneic hematopoietic cell transplantation, prophylaxis of graft-versus-host-disease in patients undergoing haploidentical allogeneic HCT, testicular germ cell tumors, preparative regimen for bone marrow transplantation, soft tissue sarcomas	Acute cardiomyopathy, arrhythmias, HF, pericardial effusion, myocardial ischemia, LBBB, endocardial fibrosis	Oxidative stress and inflammation in the cardiac muscle	Yes	If symptoms are severe: close monitoring and supportive care (oxygen therapy), temporarily withhold or reduce the dosage
Antitumor antibiotics	Mitomycin Bleomycin	Solid tumors - breast, lung, ovarian cancer Lymphomas	HF, damage similar to radiation-induced cardiac injury, pericarditis, acute onset of chest pain, CAD myocardial ischemia, MI	Generation of free radicals, oxidative stress, and impairment of mitochondrial function in cardiac cells	Yes (at cumulative doses > 30 mg/m^2)	If the acute onset of substernal chest pain: supportive; discontinuation of the drug is not needed

Monoclonal antibodies	Rituximab (targeting the CD20 antigen) Alemtuzumab (targeting the CD52 antigen)	B-cell hematological malignancies / CD 20+), malignant and benign hematologic conditions. T-cell prolymphocytic leukemia, T-cell lymphomas (*mycosis fungoides*, Sézary syndrome)	Arrhythmias, angina, MI, ventricular fibrillation, and cardiogenic shock	Not known, but potential mechanisms could be related to cytokine release syndrome, hypotension	Yes (long-term cardiac toxicity with rituximab)	If significant cardiotoxicity: discontinue therapy
Topoisomerase inhibitors	Etoposide	Lymphomas, part of cisplatin-based regimens	MI, vasospastic angina	Generation of reactive oxygen species, DNA damage impairing heart function, mitochondrial dysfunction	Unclear	If significant cardiotoxicity: close monitoring, discontinue therapy
Biologic response modifiers	Interferon-alfa Interleukin-2	Chronic myeloid leukemia, melanoma, renal cell carcinoma	Myocardial ischemia and infarction, atrial and ventricular arrhythmias, SCD, reduced ejection fraction, HF	Inflammatory response, cytokine storm	No	If significant cardiotoxicity: close monitoring, discontinue therapy
Protein kinase inhibitors	TK inhibitor - brigatinib	Anaplastic lymphoma kinase-positive metastatic non-small cell lung cancer	Hypertension, AF, ventricular arrhythmias, bradycardia	Inhibition of the HERG potassium channel, which regulates the electrical activity of the heart, inhibition of the L-type calcium channel and the sodium channel, alterations in calcium handling, generation of ROS, effects on the autonomic nervous system	Unclear	If symptomatic or severe hypertension: withhold, then reduce the dosage or permanently discontinue therapy
	MAPK inhibitors - cobimetinib, trametinib, binimetinib	Metastatic or unresectable BRAF-mutated melanoma	Left ventricular dysfunction, prolongation of the QTc interval	Direct cytotoxic effects lead to necrosis and fibrosis, increased inflammation, disruption of cardiac mitochondrial function, inhibition of signaling (PI3K/AKT and MAPK) pathways critical for maintaining cardiac function, impairment of potassium channels resulting in arrhythmias	Unclear	If symptomatic heart failure: discontinue therapy
	ALK inhibitors - crizotinib, ceritinib	Anaplastic lymphoma kinase-positive metastatic non-small cell lung cancer, anaplastic large cell lymphoma, inflammatory myofibroblastic tumor	Bradycardia, QTc interval prolongation	Decrease in cardiomyocyte survival, increased production of ROS, interference with the calcium handling in cardiomyocytes affecting contractility and electrophysiological changes, mitochondrial dysfunction, inflammation in the heart	Unclear	If QTc interval exceeds > 500 msec: dose reduction, discontinue therapy
	BTK inhibitors - ibrutinib, zanubrutinib, acalabrutinib	B-cell hematological malignancies – chronic lymphocytic leukemia, Waldenström macroglobulinemia, and mantle cell, marginal zone lymphoma	Supraventricular and ventricular arrhythmias, HF, conduction disorders, hypertension, sudden death	Vascular toxicity impairing blood flow to the heart, ion channel dysfunction in the cardiac cells, apoptosis of cardiomyocytes, mitochondrial dysfunction, off-target effects	Unclear	If significant cardiotoxicity: discontinue therapy
	BCR:ABL1 TK inhibitors - imatinib, nilotinib, dasatinib, bosutinib, ponatinib, asciminib	Gastrointestinal stromal tumors, chronic myeloid leukemia with a T3151 mutation, acute lymphoblastic leukemia	HF, ischemic heart disease due to arterial occlusive events, QTc prolongation, AF, bradycardia, syncope, VT, AV blocks	Inhibiting PI3K/AKT and ERK signaling pathways important for cardiac repair, increased oxidative stress, inhibition of c-KIT, mitochondrial dysfunction	Unclear	If significant cardiotoxicity: discontinue therapy
	EGFR TK inhibitors - vandetanib, osimertinib, mobocertinib	Non-small cell lung cancers with EGFR T790M mutation	Reduced ejection fraction, HF, cardiomyopathy, prolongation of the QTc interval	Impaired cardiac contractility and relaxation by inhibiting EGFR signaling, oxidative stress, and mitochondrial dysfunction in cardiac cells, prolongation of QT interval increases the risk of arrhythmias	Unclear	If significant cardiotoxicity: discontinue therapy
	CDK 4/6 pathway inhibitor - ribociclib	Hormone-positive, advanced, or metastatic breast cancer.	Prolongation of the QTc interval	Prolonged QT intervals can lead to an increased risk of arrhythmias, reduced LVEF, vascular damage	Unclear	If QTc intervals > 480 msec: discontinue therapy
	KIT and PDGFRA inhibitor - ripretinib	Gastrointestinal stromal tumors	HF, acute left ventricular failure, left ventricular diastolic dysfunction, ventricular hypertrophy	Inhibiting enzyme activities, interfering with calcium balance in the heart, prolongation of the QT interval	Unclear	If significant cardiotoxicity: discontinue therapy
	TK inhibitor - selpercatinib	RET fusion-positive non-small cell lung cancer, medullary thyroid cancer	Prolongation in the QTc interval	Direct toxicity to cardiomyocytes, inhibition of VEGFR and PDGFR signaling, effect on ion channels	Unclear	If significant cardiotoxicity: discontinue therapy
	TK inhibitors - sorafenib, sunitinib	Advanced renal cell carcinoma, hepatocellular carcinoma, several other types of cancer, pancreatic neuroendocrine tumors	Hypertension, reduced LVEF, clinical HF	Direct toxicity to cardiomyocytes, generation of ROS, alteration of ion channels, inhibition of VEGF and PDGF factor signaling	Unclear	If significant cardiotoxicity: discontinue therapy

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Protein kinase inhibitors	BRAF inhibitors - vemurafenib, encorafenib	Metastatic melanoma	Prolongation of the QTc interval	Direct toxicity to cardiomyocytes, alterations in calcium handling, endothelial dysfunction, prolongation of QT interval	Unclear	If significant cardiotoxicity: discontinue therapy
HER2-targeted agents	Trastuzumab Lapatinib Pertuzumab Fam-trastuzumab deruxtecan Margetuximab	HER2-expressing breast cancer	HF, acute cardiac ischemia	Increased serum HER2 levels in patients with chronic HF, enhanced susceptibility to anthracycline-induced cell death, interference with the ligand-binding-induced cardioprotective pathways	No	If symptomatic heart failure: discontinue therapy
Proteasome inhibitors	Bortezomib Carfilzomib	Multiple myeloma	New onset or worsening of preexisting HF with decreased left ventricular function or myocardial ischemia	Direct toxicity by blocking the proteasome's ability to clear damaged or abnormal proteins, mitochondrial dysfunction, apoptosis, impaired autophagy, calcium handling abnormalities in cardiomyocytes	Unclear	If chest pain, shortness of breath, or palpitations: recommended dose modification or discontinuation of therapy
HDAC inhibitors	Vorinostat Romidepsin	Cutaneous T-cell lymphoma	Prolongation of the QTc interval, supraventricular, ventricular arrhythmias, non-sustained VT	Impaired mitochondrial function, increased oxidative stress, dysregulation of gene expression involved in cardiac function by removal of acetyl groups from histones, inhibition of autophagy, activation of apoptotic pathways	Not always straightforward	If chest pain, shortness of breath, or palpitations: recommended dose modification or discontinuation of therapy

Legend: PD-1 - Programmed cell Death receptor 1; **PD-L1** - Programmed cell Death Ligand 1; **CTLA-4** - Cytotoxic T Lymphocyte-associated Antigen 4; **TK** - Tyrosine Kinase; **MAPK** - Mitogen-Activated Protein Kinase; **ALK** - Anaplastic Lymphoma Kinase; **BTK** - Bruton Tyrosine Kinase; **BCR** - Breakpoint Cluster Region; **ABL1** - Abelson gene; **EGFR** - Epidermal Growth Factor; **CDK** - Cyclin-Dependent Kinase; **KIT** - C-kit Receptor Tyrosine Kinase; **PDGFRA** - Platelet-Derived Growth Factor Receptor Alpha; **BRAF** - B-Raf Proto-oncogene, Serine/Threonine Kinase; **VEGFR** - Vascular Endothelial Growth Factor; **HDAC** - Histone Deacetylase inhibitors; **HCT** - Hematopoietic Cell Transplantation; **ALK** - Anaplastic Lymphoma Kinase-positive; **IMT** - Inflammatory Myofibroblastic Tumor; **RET** - proto-oncogene, Receptor Tyrosine Kinase; **HER2** - Human Epidermal Growth factor Receptor 2; **HF** - Heart Failure; **MI** - Myocardial Infarction; **LVEF** - Left Ventricular Ejection Fraction; **AF** - Atrial Fibrillation; **SVT** - Supraventricular Tachycardia; **VT** - Ventricular Tachycardia; **LBBB** - Left Bundle Branch Block; **DNA** - Deoxyribonucleic Acid; **HERG** - potassium channel Human Ether-a-go-go Related Gene; **ROS** - Reactive Oxygen Species; **PI3K** - Phosphatidylinositol 3-Kinase; **AKT** - Activation Of TheSerine/Threonine-specific Protein Kinase; **ERK** - Extracellular-signal-Regulated Kinase; **QTc** - corrected QT interval; **AV** – Atrioventricular; **CAD** - Coronary Artery Disease; **SCD** - Sudden Cardiac Death

with proteasome inhibitors (bortezomib, carfilzomib), which are the mainstay treatment for multiple myeloma (MM) (tables 1 and 2)[4, 13].

Myocarditis

Myocarditis, a rare but potentially life-threatening cardiotoxic effect, can be induced by immune checkpoint inhibitors (ICIs) evidenced by new left ventricular impairment, active myocardial inflammation as indicated by cardiac MRI or endomyocardial biopsy, as well as elevated serum levels of the cardiac biomarkers troponin T, troponin I, brain natriuretic peptide (BNP), or N-terminal prohormone of brain natriuretic peptide (NT-proBNP). Of these biomarkers, it is worth noting that troponin I has a high sensitivity, whereas NT-proBNP is less specific for myocarditis and can be increased due to cancer-related inflammation rather than ICI-associated cardiotoxicity[8, 10, 23]. Myocarditis with ICIs may be more frequent than is generally recognized, manifesting soon after initiation of therapy (as early as two weeks), especially with combination therapy (nivolumab and ipilimumab) and progressing malignantly; nevertheless, it is responsive to higher dosages of steroids (table 1)[8-25]. Moreover, tachyarrhythmias or bradycardia can develop with ICI-related myocarditis; therefore, electrocardiogram (ECG) monitoring is reasonable in such cases[22]. Another effect is myocarditis induced by pembrolizumab, which is attributed to CD8+ cell infiltration observed on myocardial biopsy, indicating that T-cells rather than antibodies are implicated in cardiotoxicity[8].

Pericarditis

Infrequent cardiac toxicity following immunotherapy is pericarditis, particularly with combined programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein (CTLA-4) inhibitors, while the predisposing factors are yet unknown (table 2)[26]. In addition, pericarditis has also been reported with immune checkpoint inhibitors (ICIs), which may also occur simultaneously with myocarditis, presenting with typical chest pain and dyspnea with rapid progression to respiratory failure[22].

Arrhythmia

Anthracycline use may lead to sudden death or palpitations[15, 27]. Particularly, atrial fibrillation can be more common than heart failure in acute poisoning with anthracyclines[27]. Arrhythmias arising due to anthracycline toxicity are treated by discontinuation of the therapy as well as management of arrhythmia in the acute and long term[14, 15, 27]. Also, dose-dependent prolongation of the QTc interval has been reported with VEGF TKIs, specifically sunitinib, vandetanib, and lenvatinib[28]. Individuals who experience an increase in their QTc interval during therapy should discontinue the medication until their QTc returns to 450 ms; dosing should then be resumed at a lower dose[11, 22, 28]. Importantly, concurrent use of potent CYP3A4 (Cytochrome P450, Family 3, Subfamily A, Polypeptide 4) inhibitors, which may raise plasma concentrations of TKIs that block angiogenesis, may necessitate lowering the TKIs dose[28]. CDK4/6 inhibitors such as ribociclib, which are the standard of care in adjuvant and metastatic breast cancer therapy, also prolong the QT interval,

and those patients are monitored during the first months[13]. Furthermore, cardiac conduction disease, including atrial fibrillation, ventricular tachycardia or fibrillation, and AV, have been reported following treatment with ICIs, the highest incidence being with supraventricular arrhythmias[10, 22]. Furthermore, treatment with immune checkpoint inhibitors (ICIs) can lead to bundle branch block, complete AV, as well as a prolonged PR interval, all of which might result in cardiac arrest (table 1). Arrhythmia risk is time-dependent and is thought to be directly related to T cell-mediated cytotoxicity spurred by the use of ICIs. Finally, bradycardia and heart block have also been linked to taxanes (paclitaxel) (table 2)[13].

Hypertension

Antiangiogenic agents have been associated with the onset of hypertension[29]. Therefore, blood pressure should be carefully monitored in all patients undergoing treatment with an angiogenesis inhibitor. Moreover, VEGFR tyrosine kinase inhibitors and bevacizumab have been reported to cause abnormal structural changes in arterial walls that can lead to aortic dissections and aneurysms; thus, it is imperative that patients undergoing treatment with these medications have their hypertension under control, and in the event of otherwise unexplained chest or abdominal pain, a high index of suspicion for aortic dissection is necessary. In addition, hypertension has been reported with microtubule-targeting drugs (vinca alkaloids) (table 1)[30, 31].

Myocardial ischemia and infarction

Ischemic cardiac events are increased in patients treated with the antiangiogenic agent bevacizumab[32]. Additionally, specific VEGFR tyrosine kinase inhibitors (regorafenib, sorafenib) have been associated with myocardial ischemia and infarction[11, 32].

Furthermore, fluoropyrimidines (5-fluorouracil) have also been linked to cases of myocardial ischemia, with vasospasm being a major contributing factor, typically following topical or intraperitoneal administration of the medication[1, 33]. Detection of myocardial injury induced by 5-fluorouracil relies on the elevation of cardiac troponins[34]. Interestingly, the risk of fluoropyrimidine cardiotoxicity may be influenced by the inheritance of gene polymorphisms, specifically the dihydropyrimidine dehydrogenase (DPD) enzyme (the rate-limiting enzyme in fluorouracil catabolism)[35]. In addition, major adverse cardiac events are four times more likely to occur in patients receiving ICI treatment[22]. The myocardial infarction that occurs following ICI therapy is partly driven by ICI-associated inflammation and T cell activation-induced coronary vasculitis[10, 22]. Furthermore, the expression of the PD-1–PD-L1 doublet is upregulated in myocardial ischemia and infarction, and atherosclerosis is accelerated by PD-1 genetic deficiency[10]. Moreover, vinca alkaloids (microtubule-targeting drugs) induce myocardial damage and necroptosis, thus leading to myocardial ischemia and infarction, and other vaso-occlusive complications (table 2)[36].

Thromboembolic events

While a prior history of an arterial thromboembolic event (ATE) is not an absolute contraindication for antiangiogenic agent use, keeping a low index of suspicion for drug-related ATEs, including transient ischemic attacks, strokes, angina, and myocardial infarction, is imperative[11]. Of all the cytotoxic agents, the angiogenesis inhibitor bevacizumab, particularly, has been linked to a higher incidence of potentially fatal ATEs (table 2)[37]. Therefore, in high-risk patients with a previous thromboembolic event, concurrent anticoagulation with low-dose aspirin alongside bevacizumab is justified. Additionally, bevacizumab has been associated with an increased risk of venous thromboembolism (VTE) in cancer patients, as opposed to other VEGF-targeted therapy[38].

Echocardiographic evaluation in oncological patients

Assessment of systolic function, which is based on measuring the amplitude and speed of movement or deformation of the myocardium by measuring strain and strain rate, is gaining more and more space in oncology patients themselves.

Oncology patients undergoing chemotherapy and radiation therapy can develop cardiomyopathy not only during treatment but also years after therapy[4]. Early detection of left ventricular dysfunction and early detection, prevention, and treatment of cardiotoxicity is crucial to reduce irreversible damage to the myocardium[39]. In this context, global longitudinal strain (GLS) is a more sensitive parameter than

Table 2. Summary of different cytotoxic agents linked with specific cardiotoxic effects

CARDIOTOXIC EFFECT	CYTOTOXIC DRUGS
Heart failure, myocardial ischemia, and cardiac arrest	antiangiogenic agents, osimertinib, mobocertinib, proteasome inhibitors, interferon, interleukin-2, asciminib
Myocardial necrosis leading to dilated cardiomyopathy and heart failure	sunitinib, alemtuzumab, imatinib, trametinib, taxanes combined with anthracyclines
Arterial occlusive events	bevacizumab, ponatinib
Pericarditis	cytotoxic T lymphocyte-associated antigen 4 inhibitors, programmed cell death receptor 1 inhibitors, programmed cell death ligand 1 inhibitors, cytarabine, bleomycin
Arrhythmias	taxanes, vandetanib, vemurafenib, asciminib, ponatinib, crizotinib, nilotinib, histone deacetylase inhibitors
Prolongation of the correct QT (QTc) interval	vandetanib, osimertinib, mobocertinib, selpercatinib, eribulin, crizotinib, arsenic trioxide, BRAF inhibitors, histone deacetylase inhibitors, tyrosine kinase inhibitors targeting BCR: ABL1

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ejection fraction in the detection of early, subclinical myocardial dysfunction[40]. The recommendation of international associations is that before starting potentially cardiotoxic therapy, in addition to EF, GLS should also be determined[4]. A decrease in EF by > 10% at a value < 53% or a drop in GLS > 15% compared to the initial value indicates clinically significant cardiotoxicity[4]. Following termination of oncological treatment, the first echocardiography should be done after 6-12 months, later repeated at time intervals of 1, 2, or 5 years depending on the risk factors age, the total dose of anthracycline received, a combination of chemotherapy and radiotherapy (which represents additional risk and requires more frequent controls)[4].

Conclusion

Chemotherapy has been associated with a variety of cardiotoxic effects, including heart failure, myocarditis, pericarditis, arrhythmias, hypertension, myocardial ischemia, and infarction, as well as thromboembolic events. Close monitoring for cardiac adverse effects is indispensable in patients treated with cytotoxic agents, and the risks and benefits of the specific therapies need to be carefully weighed in an individualized manner. The link between cumulative dose and cardiotoxicity is intricate and differs based on the specific medication, treatment duration, and individual patient characteristics.

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