Am J Cancer Res 2021;11(4):1132-1147
www.ajcr.us /ISSN:2156-6976/ajcr0124087

Review Article

Cardiotoxicity of chemotherapy and targeted agents

Todd William Mudd Jr[1], Mansoor Khalid[2], Achuta Kumar Guddati[1]

[1]*Division of Hematology/Oncology Georgia Cancer Center, Augusta University, Augusta 30909, GA, USA;* [2]*Mercy Hospital Oklahoma City, Oklahoma 73120, OK, USA*

Received October 13, 2020; Accepted February 4, 2021; Epub April 15, 2021; Published April 30, 2021

Abstract: The evolution of cancer treatment and development of new classes of anticancer therapies have continued to revolutionize the field of oncology. New therapies including targeted agents, immunotherapies, and adoptive cell transfer have allowed for exciting survival benefit progress for patients. However, the novel nature of these therapies as well as the longer survival periods of patients receiving them has highlighted the various side effects of anticancer therapies. Cardiotoxicity has emerged as a major side effect of anticancer treatment and can present both acutely during treatment and chronically even years after treatment has been completed. This work compiles the cardiotoxic side effects of various chemotherapeutic and targeted anticancer therapies and their management.

Keywords: Cardiotoxicity, chemotherapy, targeted agents, angina

Introduction

As our understanding of cancer biology has advanced, there has been an explosion in the number of new cancer therapeutics available to clinicians to tailor treatments for patients based on a wide variety of factors. Especially exciting in the field is the development of new categories of novel, targeted therapies that have emerged from our greater understanding of the unique molecular features of cancer. This expansion of knowledge and therapeutic strategies had led to exciting progress in prolonged patient survival, but these survival advances have also highlighted the adverse effects that come with anticancer therapy, one of the most common being cardiotoxicity [1]. Cardiotoxicity can be defined in a variety of ways including diminished left ventricular ejection fraction (LVEF), damage to cardiac cells and structure, conduction abnormalities, vascular abnormalities, as well as other adverse effects that perturb normal cardiac function [2]. Groups such as the National Cancer Institute (NCI) have defined grading schemes for cardiotoxicity. The NCI defines grade I as asymptomatic biomarker elevation or imaging abnormalities, grade II/III as cardiac symptoms that present with mild to moderate exertion, grade IV as severe symptoms needing supportive care, and grade V as death due to cardiotoxicity [3]. Cancer therapy related cardiotoxicity has the potential to exhibit permanent adverse effects in patients, so clinicians must remain vigilant for early signs of diminished cardiac function, especially in patients receiving therapies that have established cardiotoxic profiles. With the rapid advancement of new therapies, it is essential to maintain an understanding of the adverse cardiac effects of new classes of anticancer drugs. Further work establishing the molecular and physiologic basis of anticancer therapy induced cardiotoxicity will allow for better tailored treatment to the unique mechanisms of each therapy's cardiotoxicity profile.

One of the hallmarks of cardiotoxic cancer therapies is direct damage to cardiomyocytes. One well established class of cardiotoxic chemotherapeutics, the anthracyclines, cause cardiotoxicity via topoisomerase II inhibition, subsequent cardiomyocyte DNA damage, and eventual cell death resulting in heart failure (HF) and other adverse effects [4]. Another recently developed class of therapies, immune checkpoint inhibitors, also cause cardiomyocyte damage, albeit through a very different mechanism of direct cell mediated damage by disinhibited

immune cells [5]. Additional cardiotoxicities are the result of more peripheral effects that can manifest in the heart such as hypertension, atherosclerosis, and ischemic events exemplified by VEGF-inhibitor induced nitric oxide signaling dysfunction and endothelial cell dysfunction [6]. Early identification of cardiotoxicity is essential for the discontinuation of the offending agent or initiation of proper therapies to prevent permanent cardiac damage.

Tables 1 and **2** provide a compilation of the cardiotoxicity and corresponding management for two general classes of anticancer therapies: broad spectrum chemotherapy and targeted agents. Broad spectrum chemotherapy agents that cause cardiotoxicity includes classes of agents such as anthracyclines and antitumor antibiotics, alkylating agents, antimetabolites, platinum-based agents, and antimicrotubular agents. Targeted agents include HER-2 inhibitors such as trastuzumab, immune checkpoint inhibitors, small molecule inhibitors, and other therapies such as CAR-T cells, all of which have associated cardiotoxicities and corresponding management guidelines.

Epidemiology of anticancer therapy cardiotoxicity

Understanding the risk of cardiotoxicity allows clinicians to better prepare for potential adverse effects related to anticancer therapy, however, clinicians must remain vigilant for signs of cardiotoxicity even in patients receiving therapies that have low rates of cardiotoxicity. The frequency of anticancer therapy cardiotoxicity varies widely between drugs and classes of therapies. The rate of anthracycline induced HF ranges between 0.2-8.7% with risk increasing as the cumulative anthracycline dose in a patient increases [7]. This increased HF risk from anthracycline therapy continues in patients monitored for over 10 years after treatment [7, 8]. The rate of HF in patients treated with trastuzumab is up to 3.8% while other chemotherapies including alkylating agents and anti-microtubular agents have cardiotoxicity rates between 7-28% for cyclophosphamide and 2.3-8% for docetaxel [8]. The introduction of targeted agents, especial VEGF inhibitors and tyrosine kinase inhibitors (TKIs) has introduced additional cardiotoxicity risk in cancer patients. Risk of cardiotoxicity in patients receiving VEGF inhibitors is 7.4% for hypertension, 1.8% for thromboembolism, 1.7% for cardiac ischemia, and 2.3% for general cardiac dysfunction [9]. Additionally, immune checkpoint inhibitor (ICI) and CAR-T cell therapies carry a lower cardiotoxicity rate of about 1-2%, but the risk of fatal adverse events due to these therapies remains [5].

Monitoring for cardiotoxicity

As there is a wide variety of cardiotoxic effects for many different anticancer therapies, proper screening and risk assessment is essential in patients initiating treatment with a therapy that presents a cardiotoxicity risk. Traditionally, 2D-echocardiography (echo) has been used to establish baseline values for left ventricular ejection fraction (LVEF) which can then be monitored to detect cardiotoxicity manifesting as reduced LVEF [10]. While cost effective and widely accessible, echo presents issues such as measurement variability and low sensitivity for subclinical damage. Cases have been reported in patients treated with TKIs who experienced cardiotoxic events without early detection by echo [11]. As a result of this diminished sensitivity, newer imagining modalities for detecting cardiotoxicity are being used such as 3D-echocardiography and cardiovascular magnetic resonance (CMR) imaging [12]. CMR imaging provides a highly accurate, reproducible evaluation of LVEF in patients and also provides further information such as left ventricle mass, myocardium fibrosis, and ischemia [12, 13]. Additionally, study of CMR imaging in a pig animal model demonstrated that CMR could detect subclinical myocardial damage indicative of doxorubicin induced cardiotoxicity before LVEF was affected. This monitoring strategy allowed for earlier intervention to prevent irreversible cardiotoxicity from occurring [13]. Additionally, patients should receive a baseline electrocardiogram (ECG) to evaluate risk of cardiac arrythmias.

Other strategies to monitor patients for cardiotoxicity and predict cardiotoxicity risk are also being studies including cardiac biomarkers and personalized genetic screening panels. Due to drawbacks associated with serial cardiac imaging studies, there has been increased interest in the use of cardiac biomarkers such as troponins, NTproBNP, and myeloperoxidase for moni-

Table 1. List of chemotherapy agents which cause cardiotoxicity

Serial No	Agent	Cardiotoxic Effect	Management	Ref
Anthracyclines and Antitumor Antibiotics				
1.	Doxorubicin	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	[4, 10, 19, 21, 30]
2.	Daunorubicin	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	[4, 10, 19, 21, 30]
3.	Mitoxantrone	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	[4, 10, 19, 21, 30]
4.	Epirubicin	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	[4, 10, 19, 21, 30]
5.	Mitoxantrone	Arrhythmia/HF	• Arrhythmias-antiarrhythmics • HF-D/C agent, ACEI, and β-blocker	[25]
6.	Bleomycin	Pericarditis/CAD/Atherosclerosis	• Pericarditis-NSAIDs, colchicine; prednisone if severe • CAD-statin, ADP receptor inhibitor, nitrate, β-blocker • Atherosclerosis-statins	[25, 54]
7.	Mitomycin C	HF	• HF-D/C agent, ACEI, and β-blocker	[25]
Alkylating agents				
1.	Cyclophosphamide	Cardiac Tamponade/Arrhythmias/HF	• Cardiac Tamponade-pericardiocentesis, dobutamine • Arrhythmias-antiarrhythmics • HF-D/C agent, ACEI, and β-blocker	[10, 25, 27]
2.	Ifosfamide	Similar to Cyclophosphamide		[10, 25]
3.	Bleomycin	Myocardial Ischemia	• Myocardial ischemia-anticoagulation, aspirin, ADP receptor inhibitor	[10, 56]
4.	Melphalan	Acute cardiomyopathy	• Acute cardiomyopathy-D/C agent, ACEI, β-blocker, cardiac glycoside	[43]
Platinum based agents				
1.	Cisplatin	HTN/CAD/Thromboembolic Events/Angina/HF/Arrythmias	• HTN-ACEI and Ca^{2+} channel blocker (CCB) • CAD-statin, ADP receptor inhibitor, nitrate, β-blocker • Thromboembolic Events-LMWH, edoxaban, or rivaroxaban • HF-D/C agent, ACEI, and β-blocker • Angina-aspirin, ADP receptor inhibitor, nitrate, β-blocker • Arrythmias-antiarrhythmics	[2, 10, 25, 54, 56]
Antimetabolites				
1.	5-fluorouracil	Angina/MI/Arrhythmias/Cardiomyopathy/HF	• General-D/C agent • Angina-aspirin, ADP receptor inhibitor, nitrate, β-blocker • MI-PCI or IV thrombolytics as per AHA guidelines • Arrhythmia-if acute and pt unstable: cardioversion or defibrillation; Long term treatment with antiarrhythmics • Cardiomyopathy-aspirin, statin, β-blocker • HF-ACEI and β-blocker	[2, 25, 30, 31, 35]

2.	Capecitabine	Similar to 5-FU		[2, 25, 31]
Antimicrotubular Agents				
1.	Paclitaxel	Arrhythmia/Heart Block/HF/HTN	• Arrhythmias-antiarrhythmics • Heart Block-monitoring; potential pacemaker placement • HF-D/C agent, ACEI, and β-blocker • HTN-ACEI and CCB	[2, 10, 30, 54]
2.	Docetaxel	Arrhythmia/Heart Block/HF	• Arrhythmias-antiarrhythmics • Heart Block-monitoring; potential pacemaker placement • HF-D/C agent, ACEI, and β-blocker	[2, 10, 25, 30]
3.	Vinblastine	Angina/MI	• Angina-aspirin, ADP receptor inhibitor, nitrate, β-blocker • MI-PCI or IV thrombolytics as per AHA guidelines	[10, 56]

Table 2. List of targeted agents that cause cardiotoxicity

Serial No	Agent	Cardiotoxic Effect	Management	Reference
HER-2 Inhibitors				
1.	Trastuzumab	LV Dysfunction/HF/HTN/Arrythmias	• LV Dysfunction-D/C agent, ACEI, and β-blocker • HF-D/C agent, ACEI, and β-blocker • HTN-ACEI and CCB • Arrhythmias-antiarrhythmics	[2, 42, 43, 54]
2.	Pertuzumab	LV Dysfunction	• LV Dysfunction-D/C agent, ACEI, and β-blocker	[42, 54]
Checkpoint Inhibitors				
1.	Nivolumab	Myocarditis/Pericarditis/HF/Ventricular Arrhythmia	• Myocarditis-D/C agent, steroids • Pericarditis-D/C agent, pericardiocentesis • HF-D/C agent, ACEI, and β-blocker • Ventricular arrythmia-D/C agent, β-blocker; emergency defibrillation	[5, 43, 48, 55]
2.	Ipilimumab	Myocarditis/Pericarditis/HF	• Myocarditis-D/C agent, steroids • Pericarditis-D/C agent, pericardiocentesis • HF-D/C agent, ACEI, and β-blocker	[5, 43, 48, 55]
3.	Pembrolizumab	Myocarditis/HF	• Myocarditis-D/C agent, steroids • HF-D/C agent, ACEI, and β-blocker	[5, 43, 55]
4.	Atezolizumab	MI	• MI-D/C agent, PCI or IV thrombolytics as per AHA guidelines	[5, 56]
5.	Avelumab	Myocarditis/HF/Ventricular arrythmia	• Myocarditis-D/C agent, steroids • HF-D/C agent, ACEI, and β-blocker • Ventricular arrythmia-D/C agent, β-blocker; emergency defibrillation	[5, 55]
6.	Durvalumab	Myocarditis/HF/Ventricular arrythmia	• Myocarditis-D/C agent, steroids • HF-D/C agent, ACEI, and β-blocker • Ventricular arrythmia-D/C agent, β-blocker; emergency defibrillation	[5, 55]
Small molecule TKIs and VEGF-inhibitors				
1.	Sunitinib	HF/HTN/Thromboembolic events	• HF-D/C agent, ACEI, and β-blocker • HTN-ACEI and CCB • Thromboembolic Events-LMWH, edoxaban, or rivaroxaban	[2, 30, 54, 56]
2.	Sorafenib	HTN/Thromboembolic events/LV dysfunction	• HTN-ACEI and CCB • Thromboembolic Events-LMWH, edoxaban, or rivaroxaban • LV dysfunction-D/C agent, ACEI, and β-blocker	[60, 79]

3.	Regorafenib	HTN/Myocardial Ischemia	• HTN-ACEI and CCB • Myocardial ischemia-anticoagulation, aspirin, ADP receptor inhibitor	[58]
4.	Bevacizumab	HTN/HF/Thromboembolic events	• HTN-ACEI and CCB • HF-D/C agent, ACEI and β-blocker • Thromboembolic Events-LMWH, edoxaban, or rivaroxaban	[2, 10, 54, 56]
5.	Imatinib	Thromboembolic events/HTN/HF	• Thromboembolic Events-LMWH, edoxaban, or rivaroxaban • HTN-ACEI and CCB • HF-D/C agent, ACEI and β-blocker	[10, 30, 54, 56]
6.	Dasatinib	Thromboembolic events/HTN/HF	• Thromboembolic Events-LMWH, edoxaban, or rivaroxaban • HTN-ACEI and CCB • HF-D/C agent, ACEI and β-blocker	[10, 30, 54, 56]
7.	Erlotinib	Thromboembolic events/HTN	• Thromboembolic Events-LMWH, edoxaban, or rivaroxaban • HTN-ACEI and CCB	[30, 54, 56]
8.	Nilotinib	Thromboembolic events/HTN/HF/Arrhythmias	• Thromboembolic Events-LMWH, edoxaban, or rivaroxaban • HTN-ACEI and CCB • HF-D/C agent, ACEI, and β-blocker • Arrhythmias-antiarrhythmics	[10, 30, 54, 56]
9.	Ponatinib	HTN/HF/Thromboembolic Events	• Thromboembolic Events-LMWH, edoxaban, or rivaroxaban • HTN-ACEI and CCB • HF-D/C agent, ACEI, and β-blocker	[6, 10, 54, 56]
10.	Lapatinib	HF/HTN/Arrhythmias	• HF-D/C agent, ACEI, and β-blocker • HTN-ACEI and CCB • Arrhythmias-antiarrhythmics	[10, 54]
11.	Dabrafenib	Arrythmia	• Arrhythmias-antiarrhythmics	[56]
12.	Trametinib	HF	• HF-D/C agent, ACEI, and β-blocker	[56, 61]
13.	Vemurafenib	HF	• HF-D/C agent, ACEI, and β-blocker	[62]
Proteasome Inhibitors				
1.	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	[2, 10, 66]
2.	Carfilzomib	HF/Arrhythmias/Cardiomyopathy/HTN	• HF-D/C agent, ACEI, and β-blocker • Arrhythmias-antiarrhythmics • Cardiomyopathy-aspirin, statin, β-blocker • HTN-ACEI and CCB	[2, 10, 67]
3.	Ixazomib	HF	• HF-D/C agent, ACEI, and β-blocker	[68]
Other Targeted Agents and Immunomodulators				
1.	CAR-T therapy	Arrhythmia/LV dysfunction/Hypotension/HF	• General-Tocilizumab, steroids if refractory • Arrhythmias-antiarrhythmics • LV dysfunction-ACEI and β-blocker • Hypotension-fluid replacement, vasopressors • HF-ACEI and β-blocker	[6, 75, 78, 80]
2.	IL-2	Hypotension/Tachycardia/MI	• Hypotension-D/C agent, fluid replacement, vasopressors • Tachycardia-similar to hypotension • MI-PCI or IV thrombolytics as per AHA guidelines	[30, 81]

3.	Interferon	MI/Tachyarrhythmia/HF	• MI-PCI or IV thrombolytics as per AHA guidelines • Tachyarrhythmia-antiarrhythmic • HF-D/C agent, ACEI, and β-blocker	[10]
4.	Thalidomide	Thromboembolism/MI/HF/Cardiogenic shock	• Thromboembolism-LMWH, edoxaban, or rivaroxaban • MI-PCI or IV thrombolytics as per AHA guidelines • HF-D/C agent, ACEI, and β-blocker • Cardiogenic shock-D/C agent, dobutamine, norepinephrine	[10, 56]
4.	Lenalidomide	Similar to Thalidomide		

toring of cardiotoxicity and detection of subclinical damage that would not be detected with LVEF evaluation [14, 15]. Different biomarkers can be used to screen for various manifestations of cardiotoxicity such as troponins for therapy induced acute coronary syndrome (ACS) and checkpoint inhibitor induced myocarditis, D-dimers for evaluation of thromboembolic events, and BNP/NT-proBNP for HF [16]. Recently, groups have begun to perform genome-wide association studies and candidate gene analysis to identify genetic risk factors in patients who experience cardiotoxicity [17, 18]. Interestingly, single-nucleotide-polymorphisms in ATP-binding-cassette transporter genes that play a role in transmembrane doxorubicin transport and carbonyl-reductase genes that catalyze metabolism of damaging aldehydes and ketones were found to be associated with increased cardiotoxicity risk, suggesting that genetic factors do indeed contribute to increased cardiotoxicity susceptibility [17]. As of now, the best approach for cardiotoxicity monitoring in patients should employ a variety of modalities to ensure that toxicities are detected early to ensure that proper management is initiated to prevent irreversible cardiac damage.

Cardiotoxicity of broad-spectrum chemotherapy classes

Anthracyclines and antitumor antibiotics

Anthracyclines are some of the most cardiotoxic and widely used chemotherapeutic agents with use in the treatment of a variety of malignancies including lymphomas, leukemias, breast cancer, and sarcomas. The cardiotoxic effects of anthracyclines include LVEF dysfunction that can progress to HF as well as cardiac arrythmias [4, 7, 19]. Anthracycline-induced cardiotoxicity is due to a variety of mechanisms including the generation of reactive oxygen species (ROS) in cardiomyocytes, pathological changes in the metabolism of iron, and the inhibition of topoisomerase IIβ. Topoisomerase IIβ inhibition results in cardiomyocyte mitochondrial dysfunction, ROS formation, and activation of apoptosis pathways and is thought to be the primary mechanism of anthracycline induced cardiotoxicity [20]. As previously mentioned, anthracyclines carry a cardiotoxicity risk of up to 8.7% and the risk of toxicity increases exponentially as the cumulative received dose in a patient increases [7, 8].

Due to the well characterized cardiotoxicity profile of anthracyclines, there has been great interest and study into strategies to detect and manage anthracycline induced cardiotoxicity. While monitoring for is essential, study of pharmacologic management of anthracycline cardiotoxicity, especially HF, has determined that treatment with carvedilol (β-blocker) and enalapril (ACE-inhibitor) is most effective [10, 21]. Dexrazoxane administration presents another strategy to prevent anthracycline induced cardiotoxicity via iron chelation and reduced ROS production and it was found that dexrazoxane administration increases the anthracycline dose that can be given in pediatric patients before the risk of cardiotoxicity increases exponentially [22]. However, dexrazoxane does potentially diminish the antineoplastic activity of anthracyclines when co-administered [23]. Currently, dexrazoxane is recommended when high anthracycline doses are planned on being administered to a patient [24]. Looking toward the future, characterization of genetic risk factors for anthracycline-induced cardiotoxicity could allow clinicians to screen patients for their risk level. For example, candidate gene analysis has identified alleles that are associated with increased risk of anthracycline-induced cardiotoxicity, showing how future study could form genotyping panels to stratify patients into cardiotoxicity risk groups [17]. Continued development of personalized genetic screening panels for anthracycline induced cardiotoxicity risk could allow for stratification of patients and tailored treatment plans based on their risk profile.

Alkylating agents

Alkylating agents cause a variety of cardiotoxicities with the nitrogen mustards, cyclophosphamide and ifosfamide, exhibiting the most diverse profile of toxicities ranging from cardiac arrhythmias, tamponade, and HF [25]. Cyclophosphamide induced cardiotoxicity occurs primarily through its metabolism to acrolein, which then causes cardiomyocyte inflammation, ROS formation, and reduced endothelial nitric oxide synthase activity and production. Additionally, acrolein causes caspase activation and subsequent apoptosis in cardiomyo-

cytes as well as calcium overload resulting in HF [26]. Clinicians must be vigilant for cyclophosphamide-induced cardiotoxicity with a recent case report of toxicity in a bone marrow transplant patient who experienced acute, fatal HF after cyclophosphamide treatment without any previous signs of cardiac dysfunction via imaging or biomarker screening [27]. Treatment for cyclophosphamide and alkylating agent induced cardiotoxicity generally follows established treatments such as antiarrhythmics for arrhythmias, dobutamine and pericardiocentesis for tamponade, and ACE-inhibitors and β-blockers for HF [10].

Platinum based agents

Cisplatin induced cardiotoxicity has been reported in a variety of cases with toxicity ranging from hypertension and coronary artery disease (CAD) to arrhythmias and HF [2, 25]. The mechanism for cisplatin-induced cardiotoxicity includes direct toxicity to cardiomyocytes and ROS production that results in inflammation and thrombus formation [25]. One example of cisplatin-induced cardiotoxicity involves a case of a patient who received cisplatin and experienced angina with LVEF decline without an increase in cardiac biomarkers, highlighting the need for a wide variety of monitoring tests to detect cisplatin cardiotoxicity. The patient's cardiac function improved after discontinuation of cisplatin administration [28]. Another recent example of cisplatin induced cardiotoxicity involves a case of a patient who received cisplatin and then suffered from multiple myocardial infarctions secondary to acute thrombotic events potentially due to cisplatin administration. The first MI occurred during therapy administration while the second occurred ten months after chemotherapy, indicating that patients must be monitored for long term cardiotoxicity [29]. Treatments for cisplatin induced cardiotoxicity typically follows accepted guidelines for the specific cardiac disease as shown in **Table 1**.

Antimetabolite agents

Within the antimetabolite class of chemotherapeutic agents, 5-florouracil (5-FU) and capecitabine, a prodrug that is metabolized to 5-FU, are the most cardiotoxic. As they both share a metabolic pathway, administration of the two drugs can result in similar cardiotoxic effects. 5-FU (and capecitabine) induced cardiotoxicity includes angina, ventricular tachycardia, MI, cardiomyopathy, and HF [2, 30, 31]. 5-FU induced cardiotoxicity results from multiple mechanisms including coronary artery effects and direct effects on cardiomyocytes. 5-FU and its metabolites can cause oxidative stress in coronary artery vascular smooth muscle resulting in vasospasm and thrombosis, and they also can induce direct damage of cardiomyocytes via disruption of mitochondrial function and activation of apoptosis [31]. All these effects can be seen after administration of the first dose of 5-FU. Switching to a bolus dose from a continuous infusion regimen has been shown to mitigate the vaso-spastic effects of 5-FU. Many case reports describe the wide variety of cardiotoxicities that can occur in patients receiving 5-FU including cases describing angina secondary to coronary vasospasm, atrial fibrillation, and acute cardiomyopathy [32-34]. In each of the cases, clinicians were able to successfully treat the cardiotoxicity with discontinuation of 5-FU, and subsequent treatment for the individual cardiac conditions following established protocols. Another case in the literature describes a patient who experienced acute Takotsubo cardiomyopathy 4 days after starting capecitabine, highlighting how capecitabine's metabolism into 5-FU results in similar cardiotoxicities with each drug [35]. As with the other cases mentioned, the patient recovered with discontinuation of the capecitabine and treatment for the Takotsubo cardiomyopathy with a statin, aspirin, and β-blocker. Pre-treatment with isosorbide mononitrate and post-treatment with nifedipine has also been recommended to alleviate cardiotoxicity. Other cardiotoxicities of 5-FU and capecitabine and their treatments are included in **Table 1**.

Antimicrotubular agents

While antimicrotubular agents such as the taxanes cause cardiotoxicities that include heart block, hypertension, arrythmias, and CHF, recent study of taxane cardiotoxicity has explored if they exacerbate toxicity of other chemotherapy drugs such as anthracyclines or trastuzumab [2, 30]. The mechanism of taxane-induced cardiotoxicity is not well characterized, but studies suggest that it may be due to disruption of the cardiac Purkinje fiber

system or disruption of autonomic control of the cardiac electrical circuit [25]. The additive cardiotoxicity risk between taxanes, anthracyclines, and trastuzumab has been of interest due to the well characterized cardiotoxicity of anthracyclines and trastuzumab and their concomitant use in chemotherapy regimens. Meta-analysis of toxicities in patients treated with anthracyclines alone vs. anthracycline and taxane therapy found that patients treated with anthracyclines alone had a higher rate of cardiotoxicity vs. patients treated with combination therapy [36]. Additional study of paclitaxel administered in a chemotherapy regimen with Trastuzumab and Pertuzumab found that the combination therapy did not pose a higher cardiotoxicity risk while improving survival outcomes [37]. More recently, study of combination therapy of Pertuzumab, trastuzumab, taxane, and then either ddAC (dose denset adriamycin plus cyclophosphamide) or FEC (5-FU, Epirubicin, cyclophosphamide) found no significant cardiotoxicity differences between the two treatment groups [38]. Overall, taxanes carry a low but still significant cardiotoxicity risk that clinicians must monitor for, especially when administered in addition to other more cardiotoxic drugs. Treatment for taxane related cardiotoxicity follows established guidelines for the individual toxicity as outlined in **Table 1**.

Cardiotoxicity of targeted agents

HER-2 inhibitors

HER-2 or *human epidermal growth factor receptor 2* is an oncogene whose pathologic amplification is used as a major classifier in breast cancer for individualizing treatment for patients [39]. Amplification of HER-2 results in over-activation of cellular growth, proliferation, and cell survival via the PI3K-AKT-mTOR-RAS-MAPK signaling pathway [30]. The development of targeted therapies that inhibit HER-2, such as trastuzumab, have greatly improved the prognosis of HER-2 positive breast cancer [40]. More recent work is also exploring whether HER-2 inhibitors improve survival in other HER-2 positive tumors such as colorectal cancer, gallbladder carcinoma, non-small cell lung cancer, and bladder cancer [41]. While anti-HER-2 therapies such as trastuzumab have improved outcomes in HER-2 positive breast cancer, they also have considerable cardiotoxicities including LV dysfunction with reduced LVEF, cardiac arrhythmias, HTN, and HF [42, 43].

Blockage of HER-2 signaling by trastuzumab in cardiomyocytes results in ROS production, disruption of mitochondrial function, and induction of pro-apoptotic signaling ultimately manifesting clinically as HER-2-inhibitor induced cardiotoxicity [44, 45]. Trastuzumab induced cardiotoxicity is well characterized and a meta-analysis of over 29,000 female patients treated with trastuzumab found that about 3% of patients experienced severe cardiotoxicity due to trastuzumab administration [46]. More recent study has focused on the management and prevention of trastuzumab induced cardiotoxicity. In a randomized, double-blinded, placebo-controlled trial comparing preventative lisinopril vs carvedilol vs placebo, Guglin et al found that there was no statistically significant difference in cardiotoxicity rates between all three prevention groups in patients receiving trastuzumab alone. In patients treated with trastuzumab with an anthracycline, Guglin et al found that preventative administration of lisinopril or carvedilol each resulted in lower cardiotoxicity rates compared with placebo [47]. The results of this study highlight how the cardiotoxicity of individual drugs within a cancer treatment regimen can be managed successfully as well as the need for more prospective studies to develop preventative treatment strategies for trastuzumab induced cardiotoxicity so that treatment can be proactive instead of reactive to adverse events.

Immune checkpoint inhibitors

One of the most exciting new advances in anticancer therapy are immune checkpoint inhibitors (ICIs) which mediate an antitumor effect by blocking immunoregulatory signaling via inhibition of immune function attenuating molecules including CTLA-4 and PD-1. In doing so, ICIs unleash disinhibited immune cells to destroy tumor cells, but this disinhibition brings the additional effect of autoimmune attack of self-tissues, including cardiomyocytes. Many case reports of severe ICI-related cardiotoxicities have been published, including fatal events. Altan et al reported three cases of patients who experienced pericarditis secondary to ICI therapy with either anti-PD-1 therapy or combination anti-PD-1 and anti-CTLA-4 therapy [48]. Notably, the two fatal cases were patients

who received combination anti-PD-1 and anti-CTLA-4 therapy which is consistent with observations that cardiotoxicity rates were higher in patients who received dual ICI therapy vs single agent ICI therapy [5, 49]. Other fatal cases of HF in patients receiving nivolumab have been reported [50, 51]. Recent meta-analysis by Rahouma et al found that anti-PD-1/PD-L1 ICI treatment had cardiotoxicity rates that were not significantly different than other therapies and Mahmood et al reported an ICI-associated myocarditis rate of about 1.4% indicating that ICI-related cardiotoxicity presents at a rate similar to or lower than other chemotherapies, however, the severe nature of ICI-related cardiotoxicity requires close monitoring and the development of proactive and effective management plans [52, 53].

Surveillance for myocarditis and other adverse cardiac events in these patients receiving ICI therapy is essential and can be done using a combination of methods previously mentioned including serological evaluation of troponin levels and cardiac imaging such as echo or CMR [10, 16]. Treatment protocols developed for cases of ICI-related myocarditis are similar to acute organ transplant rejection and involve immediate discontinuation of the agent, initiation of high dose steroids, non-steroid immunosuppressants if the myocarditis is refractory to steroids, and eventual tapering of immunosuppressant treatment with steroids [5, 54, 55]. Treatment of resultant sequela from ICI therapy such as heart failure with established treatments such as ACE-inhibitors (ACEI) and β-blockers, similar to how cardiotoxicity from other anticancer therapies is managed [5, 54]. As ICI therapy becomes more widely used, future study to predict genetic risk factors for predisposition to ICI-related cardiotoxicity such as myocarditis is essential to properly tailor treatment for each individual patient. In addition to risk stratification, preventative measures that can balance between blocking autoimmune hyperactivity in tissues such as the heart while maintaining the potent antitumor activity of immunotherapies can hopefully lessen the burden of toxicities associated with ICIs and other anticancer immunotherapies.

Small molecule TKIs and VEGF-inhibitors

VEGF and small molecule tyrosine kinase inhibitors (TKIs) represent a recently developed class of targeted anticancer therapies that exhibit cardiotoxic adverse effects. These therapies inhibit a wide variety of tumor associated targets that mediate growth and angiogenesis but are also associated with cardiotoxicities that range from hypertension (HTN), thromboembolic events, HF, and arrhythmias [2, 10, 56]. Cardiotoxicity due to VEGF inhibitors is due to a variety of mechanisms including acceleration of atherosclerosis, impaired ability for coronary vasculature to respond to myocardial ischemia, and induction of hypertension via increased vascular resistance leading to ventricular hypertrophy [57]. As previously stated, risk of cardiotoxicity in patients receiving VEGF inhibitors is 7.4% for hypertension, 1.8% for thromboembolism, 1.7% for cardiac ischemia, and 2.3% for general cardiac dysfunction [9, 57]. Small molecule TKI related cardiotoxicity occurs in a variety of mechanisms that are specific to the individual inhibitor and its target, but all commonly cause toxicity via cardiomyocyte damage. One example is the TKI regorafenib, which causes cardiotoxicity via impairment of cardiomyocyte mitochondrial ATP production and disruption of mitochondrial membrane potential [58]. Analysis of the wide range of small molecule TKIs, found that 73% have reported cardiotoxicities ranging from arrhythmias, HTN, LVEF dysfunction, HF, and myocardial infarction (MI) [59].

A variety of cases have been published reporting cardiotoxicity due to VEGF inhibitors and TKIs including fatal myocarditis due to sorafenib treatment and heart failure in a patient treated with trametinib [60, 61]. Another case report described HF due to vemurafenib treatment that was successfully reversed with discontinuation of vemurafenib and pharmacologic treatment of the HF, highlighting the potential for small molecule inhibitor cardiotoxicity to be successfully reversed if caught early and treated properly [62]. Common surveillance findings that indicate VEGF inhibitor and TKI therapy related cardiotoxicity include QT prolongation and other ECG abnormalities indicative of arrhythmias or acute MI, elevated d-dimers indicative of thromboembolism, and signs of heart failure such as elevated BNP [9, 16, 59]. Imaging such as CMR and electrocardiography are also essential for early detection of signs of LVEF dysfunction and HF [16]. General treatment for each cardiotoxicity follows established guidelines as outlined in **Table 2**, but fur-

ther study and future development of therapies that are more target specific have the potential to reduce the cardiotoxic profile of these effective anticancer therapies. Additionally, more study into predictive risk stratification of patients receiving these therapies will allow for more targeted monitoring of at-risk patients and preparation for therapeutic intervention when necessary.

Proteasome inhibitors

Proteasome inhibitors include bortezomib, carfilzomib, and ixazomib, the most recently approved agent within the class. They have been widely used in the treatment of multiple myeloma and exhibit anticancer activity via inhibition of the 20S core of the proteasome leading to impaired cancer cell degradation of pro-apoptotic molecules and subsequent destruction of cancer cells [63]. Cardiotoxicity secondary to proteasome inhibitor treatment occurs due to a host of downstream effects secondary to cardiomyocyte proteasome inhibition including endoplasmic reticulum stress due to protein accumulation, protein aggregation leading to inclusion body formation, caspase and apoptosis activation, and pathologic cardiomyocyte hypertrophy [64, 65]. Proteasome inhibitor cardiotoxicity has been well characterized with retrospective analysis for bortezomib finding cardiotoxicity rates of up to 7.6% for HF, 5.6% for arrhythmias, 2.9% for ischemic heart disease, and 13.5% for hypertension [66]. For carfilzomib, analysis of phase II trial data found cardiotoxicity rates of 13.3% for arrhythmia, 7.2% for HF, 3.4% for ischemic heart disease, and 1.7% for cardiomyopathy [67].

While large, trial-based cardiotoxicity analysis of ixazomib has not been studied, case reports of ixazomib cardiotoxicity have been published including a report of a patient who suffered from acute HF secondary to treatment with ixazomib suggesting that cardiotoxicity is an overall drug class effect of proteasome inhibitors [68]. The clinicians discontinued the ixazomib, and administered carvedilol, spironolactone, and furosemide but the patient's heart function did not improve. Similar to the management of ixazomib cardiotoxicity, treatment for cardiotoxicities of other proteasome inhibitors follows established treatment for the cardiac dysfunction as outlined in **Table 2**. For example, a patient who experienced HF while receiving bortezomib was treated for the HF and then improved their LVEF, though it did not fully recover to the baseline value [69]. There is also a report of a multiple myeloma patient who experienced cardiotoxicity when receiving both carfilzomib and the immunomodulator lenalidomide suggesting that each drug class in multiple myeloma treatment may act synergistically to cause cardiotoxicity [70]. As proteasome inhibitors continue to be developed and employed as treatment for multiple myeloma, new prevention strategies and risk prediction must be developed to address the well characterized cardiotoxicity of this class of anticancer therapy.

CAR-T cells

CAR-T cells represent a paradigm shift in anticancer therapy that has revolutionized the treatment of malignancies such as lymphoma and leukemia. Similar to ICI therapies, CAR-T cells harness the immune system to destroy malignant cells but instead of a mechanism involving disinhibition of the immune response, CAR-T cells are patient derived T-cells that have been engineered to target specific antigens on malignant cells, such as CD19 [71]. In addition to being approved for treatment of hematologic malignancies, CAR-T cells are also being widely studied for solid malignancies and represent a rapidly advancing therapeutic strategy that is growing in use [72]. One of the most common and striking side effects of CAR-T therapy is cytokine release syndrome (CRS) which is clinically characterized by fever, flu-like symptoms, circulatory shock and hypotension, and even multi-organ failure [73]. Of note in regard to this review, data indicating CAR-T cell therapy mediated cardiotoxicity, especially secondary to CRS, has been published and includes toxicities such as arrythmias, HF, and cardiovascular related deaths [74, 75].

In a retrospective cohort study of adult patients receiving CAR-T cell therapy, Raza et al found that 17 out of 137 patients experienced cardiotoxicity (12.4%) including 5 patients with arrythmia, 6 with HF, and 6 who died from cardiotoxicity. Of note, each patient in the study who experienced cardiotoxicity after CAR-T cell adminis-

tration also experienced grade 2 or higher CRS before the cardiotoxicity, indicating that CAR-T related cardiotoxicity likely occurs secondarily to CRS. Additionally, Raza et al found that all but one patient who experienced cardiotoxicity also had elevated troponin levels, suggesting that the combination of grade 2 or higher CRS with elevated troponins was highly indicative of potential for CAR-T cell induced cardiotoxicity [75]. These findings were consistent with another retrospective study by Shalabi et al of pediatric and young adult patients receiving CAR-T cells which found that 6 of 52 patients in the study experienced cardiotoxicity with reduced LVEF. As in the adult study, the cardiotoxicity was secondary to CRS in the 6 patients with 4 of the 6 patients also having elevated troponin levels [76]. These findings necessitate the close monitoring of troponin levels in patients receiving CAR-T cell therapy, especially those who experience CRS after therapy administration. IL-6 is an inflammatory cytokine that has been identified as a major factor in the development of CRS secondary to CAR-T cell therapy and administration of Tocilizumab, an anti-IL-6 mAb, is used in severe cases of CRS [77]. The likely connection between CRS progression and severity with cardiotoxicity in patients receiving CAR-T cells has led to consideration of Tocilizumab as a potential preventative treatment for CAR-T cardiotoxicity, however, concerns over potential deleterious effects of Tocilizumab on the anticancer activity of CAR-T cells calls for further study of it as a treatment for CAR-T cell induced cardiotoxicity [78]. As CAR-T cell therapy becomes more widespread, clinicians must be prepared for the varieties of toxicities the therapy presents including CRS and cardiotoxicity. Additionally, longitudinal study to characterize long term cardiotoxic effects of CAR-T therapy in survivors will be necessary as patient outcomes improve in durability.

Conclusions

While the management of anticancer treatment cardiotoxicity is a current topic of intense study, there are few evidence-based guidelines for treatment related adverse cardiotoxic events. Many mainstays of cancer treatment such as alkylating agents, antimetabolites, platinum agents, and antimicrotubular agents exhibit cardiotoxic effects such as arrhythmias, HF, and myocardial ischemia [2, 25]. Management of these adverse effects still involves following treatment guidelines that have been established for patients diagnosed with these conditions outside the scope of a treatment related adverse effect [56]. The lack of established guidelines highlights the importance of a close collaboration between oncology and cardiology for patient management including patient risk profiling, screening for cardiotoxicity, cancer treatment regimen management, and management of acute and chronic manifestations of treatment related cardiotoxicity.

The rapid advance and development of targeted anticancer agents has greatly expanded our ability to effectively treat a wide variety of malignancies, but also requires oncologists to remain well informed of the associated toxicities with these treatments. Cancer therapy related cardiotoxicity remains a major challenge and surveillance for signs of treatment related cardiotoxicity and corresponding management are essential. This is highlighted by the development and expansion of the field of cardio-oncology. While most treatments for therapy related cardiotoxicity follow previously established guidelines for conditions such as HTN, arrhythmias, and thromboembolic events, oncologists and cardiologists must continue to monitor new guidelines as they are developed and evaluated in clinical trials. Proactive monitoring of patient's cardiac function and early intervention once signs of cardiotoxicity are present will allow for delivery of the best care possible for patients.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Achuta Kumar Guddati, Division of Hematology/Oncology, Georgia Cancer Center, Augusta University, Augusta 30909, GA, USA. Tel: 312-404-8928; E-mail: aguddati@augusta.edu

References

[1] Conway A, McCarthy AL, Lawrence P and Clark RA. The prevention, detection and management of cancer treatment-induced cardiotoxicity: a meta-review. BMC Cancer 2015; 15: 366.

[2] Lenneman CG and Sawyer DB. Cardio-oncology: an update on cardiotoxicity of cancer-related treatment. Circ Res 2016; 118: 1008-1020.

[3] Perez IE, Taveras Alam S, Hernandez GA and Sancassani R. Cancer therapy-related cardiac dysfunction: an overview for the clinician. Clin Med Insights Cardiol 2019; 13: 1-11.
[4] Vejpongsa P and Yeh ET. Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. J Am Coll Cardiol 2014; 64: 938-945.
[5] Lyon AR, Yousaf N, Battisti NML, Moslehi J and Larkin J. Immune checkpoint inhibitors and cardiovascular toxicity. Lancet Oncol 2018; 19: e447-e458.
[6] Dong J and Chen H. Cardiotoxicity of anticancer therapeutics. Front Cardiovasc Med 2018; 5: 9.
[7] Volkova M and Russell R 3rd. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. Curr Cardiol Rev 2011; 7: 214-220.
[8] Curigliano G, Cardinale D, Dent S, Criscitiello C, Aseyev O, Lenihan D and Cipolla CM. Cardiotoxicity of anticancer treatments: epidemiology, detection, and management. CA Cancer J Clin 2016; 66: 309-325.
[9] Touyz RM and Herrmann J. Cardiotoxicity with vascular endothelial growth factor inhibitor therapy. NPJ Precis Oncol 2018; 2: 13.
[10] Finet JE and Tang WHW. Protecting the heart in cancer therapy. F1000Res 2018; 7: F1000 Faculty Rev-1566.
[11] Skubitz KM. Cardiotoxicity monitoring in patients treated with tyrosine kinase inhibitors. Oncologist 2019; 24: e600-e602.
[12] Seraphim A, Westwood M, Bhuva AN, Crake T, Moon JC, Menezes LJ, Lloyd G, Ghosh AK, Slater S, Oakervee H and Manisty CH. Advanced imaging modalities to monitor for cardiotoxicity. Curr Treat Options Oncol 2019; 20: 73.
[13] Galan-Arriola C, Lobo M, Vilchez-Tschischke JP, Lopez GJ, de Molina-Iracheta A, Perez-Martinez C, Aguero J, Fernandez-Jimenez R, Martin-Garcia A, Oliver E, Villena-Gutierrez R, Pizarro G, Sanchez PL, Fuster V, Sanchez-Gonzalez J and Ibanez B. Serial magnetic resonance imaging to identify early stages of anthracycline-induced cardiotoxicity. J Am Coll Cardiol 2019; 73: 779-791.
[14] Quatromoni N and Scherrer-Crosbie M. Update on incorporating biomarkers with imaging findings for the detection and management of cardiotoxicity. Curr Cardiol Rep 2018; 20: 67.
[15] Raluca Maniu D, Blag C, Popa G, Bota M, Vlad C, Cainap C, Balacescu O, Pop L and Cainap SS. The role of biomarkers and echocardiography in the evaluation of cardiotoxicity risk in children treated for leukemia. J BUON 2018; 23: 122-131.
[16] Michel L, Rassaf T and Totzeck M. Biomarkers for the detection of apparent and subclinical cancer therapy-related cardiotoxicity. J Thorac Dis 2018; 10: S4282-S4295.
[17] Leong SL, Chaiyakunapruk N and Lee SW. Candidate gene association studies of anthracycline-induced cardiotoxicity: a systematic review and meta-analysis. Sci Rep 2017; 7: 39.
[18] Nakano MH, Udagawa C, Shimo A, Kojima Y, Yoshie R, Zaha H, Abe N, Motonari T, Unesoko M, Tamura K, Shimoi T, Yoshida M, Yoshida T, Sakamoto H, Kato K, Mushiroda T, Tsugawa K and Zembutsu H. A genome-wide association study identifies five novel genetic markers for trastuzumab-induced cardiotoxicity in Japanese population. Biol Pharm Bull 2019; 42: 2045-2053.
[19] McGowan JV, Chung R, Maulik A, Piotrowska I, Walker JM and Yellon DM. Anthracycline chemotherapy and cardiotoxicity. Cardiovasc Drugs Ther 2017; 31: 63-75.
[20] Cardinale D, Iacopo F and Cipolla CM. Cardiotoxicity of anthracyclines. Front Cardiovasc Med 2020; 7: 26.
[21] Kheiri B, Abdalla A, Osman M, Haykal T, Chahine A, Ahmed S, Osman K, Hassan M, Bachuwa G and Bhatt DL. Meta-analysis of carvedilol for the prevention of anthracycline-induced cardiotoxicity. Am J Cardiol 2018; 122: 1959-1964.
[22] Liesse K, Harris J, Chan M, Schmidt ML and Chiu B. Dexrazoxane significantly reduces anthracycline-induced cardiotoxicity in pediatric solid tumor patients: a systematic review. J Pediatr Hematol Oncol 2018; 40: 417-425.
[23] Tebbi CK, London WB, Friedman D, Villaluna D, De Alarcon PA, Constine LS, Mendenhall NP, Sposto R, Chauvenet A and Schwartz CL. Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. J Clin Oncol 2007; 25: 493-500.
[24] Reichardt P, Tabone MD, Mora J, Morland B and Jones RL. Risk-benefit of dexrazoxane for preventing anthracycline-related cardiotoxicity: re-evaluating the European labeling. Future Oncol 2018; 14: 2663-2676.
[25] Madeddu C, Deidda M, Piras A, Cadeddu C, Demurtas L, Puzzoni M, Piscopo G, Scartozzi M and Mercuro G. Pathophysiology of cardiotoxicity induced by nonanthracycline chemotherapy. J Cardiovasc Med (Hagerstown) 2016; 17 Suppl 1: S12-18.
[26] Iqubal A, Iqubal MK, Sharma S, Ansari MA, Najmi AK, Ali SM, Ali J and Haque SE. Molecular mechanism involved in cyclophosphamide-induced cardiotoxicity: old drug with a new vision. Life Sci 2019; 218: 112-131.
[27] Martin M, Fornecker LM, Marcellin L, Mousseaux E, Hij A, Snowden JA, Farge D and Martin T. Acute and fatal cardiotoxicity following high-

dose cyclophosphamide in a patient undergoing autologous stem cell transplantation for systemic sclerosis despite satisfactory cardiopulmonary screening. Bone Marrow Transplant 2017; 52: 1674-1677.
[28] Hu Y, Sun B, Zhao B, Mei D, Gu Q and Tian Z. Cisplatin-induced cardiotoxicity with midrange ejection fraction: a case report and review of the literature. Medicine (Baltimore) 2018; 97: e13807.
[29] Morrow AJ, Cameron AC, Payne AR, White J and Lang NN. Cisplatin related cardiotoxicity-acute and chronic cardiovascular morbidity in a testicular cancer survivor. Scott Med J 2020; 65: 24-27.
[30] Jain D, Russell RR, Schwartz RG, Panjrath GS and Aronow W. Cardiac complications of cancer therapy: pathophysiology, identification, prevention, treatment, and future directions. Curr Cardiol Rep 2017; 19: 36.
[31] Shiga T and Hiraide M. Cardiotoxicities of 5-fluorouracil and other fluoropyrimidines. Curr Treat Options Oncol 2020; 21: 27.
[32] Charkviani M, Murvelashvili N, Barrera F, Sharma A, Eldin RS and Nabil NUN. Rare presentation of cardiotoxicity related to 5-fluorouracil. Case Rep Oncol Med 2020; 2020: 4151474.
[33] Moriyama S, Yokoyama T, Irie K, Ito M, Tsuchihashi K, Fukata M, Kusaba H, Maruyama T and Akashi K. Atrial fibrillation observed in a patient with esophageal cancer treated with fluorouracil. J Cardiol Cases 2019; 20: 183-186.
[34] Thalambedu N and Khan Y. Fluorouracil (5-FU)-induced cardiomyopathy. Cureus 2019; 11: e5162.
[35] Bhardwaj PV, Chaubey VK and Islam AM. Capecitabine-induced takotsubo cardiomyopathy: a case report. Perm J 2019; 23: 18-245.
[36] Feng QJ, Zhang F, Huang XY and Wu ZX. Effectiveness and complications of anthracycline and taxane in the therapy of breast cancer: a meta-analysis. Pathol Oncol Res 2014; 20: 179-184.
[37] Yu AF, Manrique C, Pun S, Liu JE, Mara E, Fleisher M, Patil S, Jones LW, Steingart RM, Hudis CA and Dang CT. Cardiac safety of paclitaxel plus trastuzumab and pertuzumab in patients with HER2-positive metastatic breast cancer. Oncologist 2016; 21: 418-424.
[38] Swain SM, Ewer MS, Viale G, Delaloge S, Ferrero JM, Verrill M, Colomer R, Vieira C, Werner TL, Douthwaite H, Bradley D, Waldron-Lynch M, Kiermaier A, Eng-Wong J and Dang C; BERENICE Study Group. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. Ann Oncol 2018; 29: 646-653.
[39] Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM and Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist 2009; 14: 320-368.
[40] Pondé N, Brandão M, El-Hachem G, Werbrouck E and Piccart M. Treatment of advanced HER2-positive breast cancer: 2018 and beyond. Cancer Treat Rev 2018; 67: 10-20.
[41] Oh DY and Bang YJ. HER2-targeted therapies - a role beyond breast cancer. Nat Rev Clin Oncol 2020; 17: 33-48.
[42] Jerusalem G, Lancellotti P and Kim SB. HER2+ breast cancer treatment and cardiotoxicity: monitoring and management. Breast Cancer Res Treat 2019; 177: 237-250.
[43] Payne DL and Nohria A. Prevention of chemotherapy induced cardiomyopathy. Curr Heart Fail Rep 2017; 14: 398-403.
[44] Leemasawat K, Phrommintikul A, Chattipakorn SC and Chattipakorn N. Mechanisms and potential interventions associated with the cardiotoxicity of ErbB2-targeted drugs: insights from in vitro, in vivo, and clinical studies in breast cancer patients. Cell Mol Life Sci 2020; 77: 1571-1589.
[45] Nemeth BT, Varga ZV, Wu WJ and Pacher P. Trastuzumab cardiotoxicity: from clinical trials to experimental studies. Br J Pharmacol 2017; 174: 3727-3748.
[46] Mantarro S, Rossi M, Bonifazi M, D'Amico R, Blandizzi C, La Vecchia C, Negri E and Moja L. Risk of severe cardiotoxicity following treatment with trastuzumab: a meta-analysis of randomized and cohort studies of 29,000 women with breast cancer. Intern Emerg Med 2016; 11: 123-140.
[47] Guglin M, Krischer J, Tamura R, Fink A, Bello-Matricaria L, McCaskill-Stevens W and Munster PN. Randomized trial of lisinopril versus carvedilol to prevent trastuzumab cardiotoxicity in patients with breast cancer. J Am Coll Cardiol 2019; 73: 2859-2868.
[48] Altan M, Toki MI, Gettinger SN, Carvajal-Hausdorf DE, Zugazagoitia J, Sinard JH, Herbst RS and Rimm DL. Immune checkpoint inhibitor-associated pericarditis. J Thorac Oncol 2019; 14: 1102-1108.
[49] Moslehi JJ, Salem JE, Sosman JA, Lebrun-Vignes B and Johnson DB. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. Lancet 2018; 391: 933.
[50] Sharma M, Suero-Abreu GA and Kim B. A case of acute heart failure due to immune checkpoint blocker nivolumab. Cardiol Res 2019; 10: 120-123.

[51] Sakai T, Yahagi K, Hoshino T, Yokota T, Tanabe K, Mori M and Ikeda S. Nivolumab-induced myocardial necrosis in a patient with lung cancer: a case report. Respir Med Case Rep 2019; 27: 100839.
[52] Rahouma M, Karim NA, Baudo M, Yahia M, Kamel M, Eldessouki I, Abouarab A, Saad I, Elmously A, Gray KD, Ghaly G, Gaber O, Kamal M, A Hassan A, Rahouma M, D'Ascenzo F, Morris J, Mohamed A, Girardi L and Gaudino M. Cardiotoxicity with immune system targeting drugs: a meta-analysis of anti-PD/PD-L1 immunotherapy randomized clinical trials. Immunotherapy 2019; 11: 725-735.
[53] Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, Sullivan RJ, Damrongwatanasuk R, Chen CL, Gupta D, Kirchberger MC, Awadalla M, Hassan MZO, Moslehi JJ, Shah SP, Ganatra S, Thavendiranathan P, Lawrence DP, Groarke JD and Neilan TG. Myocarditis in patients treated with immune checkpoint inhibitors. J Am Coll Cardiol 2018; 71: 1755-1764.
[54] Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, Herrmann J, Porter C, Lyon AR, Lancellotti P, Patel A, DeCara J, Mitchell J, Harrison E, Moslehi J, Witteles R, Calabro MG, Orecchia R, de Azambuja E, Zamorano JL, Krone R, Iakobishvili Z, Carver J, Armenian S, Ky B, Cardinale D, Cipolla CM, Dent S and Jordan K. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol 2020; 31: 171-190.
[55] Zhang JC, Chen WD, Alvarez JB, Jia K, Shi L, Wang Q, Zou N, He K and Zhu H. Cancer immune checkpoint blockade therapy and its associated autoimmune cardiotoxicity. Acta Pharmacol Sin 2018; 39: 1693-1698.
[56] Totzeck M, Schuler M, Stuschke M, Heusch G and Rassaf T. Cardio-oncology-strategies for management of cancer-therapy related cardiovascular disease. Int J Cardiol 2019; 280: 163-175.
[57] Touyz RM and Herrmann J. Cardiotoxicity with vascular endothelial growth factor inhibitor therapy. NPJ Precis Oncol 2018; 2: 13.
[58] Boran T, Akyildiz AG, Jannuzzi AT and Alpertunga B. Extended regorafenib treatment can be linked with mitochondrial damage leading to cardiotoxicity. Toxicol Lett 2021; 336: 39-49.
[59] Jin Y, Xu Z, Yan H, He Q, Yang X and Luo P. A comprehensive review of clinical cardiotoxicity incidence of FDA-approved small-molecule kinase inhibitors. Front Pharmacol 2020; 11: 891.
[60] Asawaeer M, Barton D, Radio S and Chatzizisis YS. Tyrosine kinase inhibitor-induced acute myocarditis, myositis, and cardiogenic shock. Methodist Debakey Cardiovasc J 2018; 14: e5-e6.
[61] Banks M, Crowell K, Proctor A and Jensen BC. Cardiovascular effects of the mek inhibitor, trametinib: a case report, literature review, and consideration of mechanism. Cardiovasc Toxicol 2017; 17: 487-493.
[62] Raftopoulos LG, Aggeli C, Zisimos K, Venieri E, Toutouzas K, Gogas H and Tousoulis D. Cardiotoxicity after vemurafenib administration. Hellenic J Cardiol 2019; 60: 256-257.
[63] Manasanch EE and Orlowski RZ. Proteasome inhibitors in cancer therapy. Nat Rev Clin Oncol 2017; 14: 417-433.
[64] Gavazzoni M, Vizzardi E, Gorga E, Bonadei I, Rossi L, Belotti A, Rossi G, Ribolla R, Metra M and Raddino R. Mechanism of cardiovascular toxicity by proteasome inhibitors: new paradigm derived from clinical and pre-clinical evidence. Eur J Pharmacol 2018; 828: 80-88.
[65] Wu P, Oren O, Gertz MA and Yang EH. Proteasome inhibitor-related cardiotoxicity: mechanisms, diagnosis, and management. Curr Oncol Rep 2020; 22: 66.
[66] Laubach JP, Moslehi JJ, Francis SA, San Miguel JF, Sonneveld P, Orlowski RZ, Moreau P, Rosiñol L, Faber Jr EA, Voorhees P, Mateos MV, Marquez L, Feng H, Desai A, van de Velde H, Elliott J, Shi H, Dow E, Jobanputra N, Esseltine D-L, Niculescu L, Anderson KC, Lonial S and Richardson PG. A retrospective analysis of 3954 patients in phase 2/3 trials of bortezomib for the treatment of multiple myeloma: towards providing a benchmark for the cardiac safety profile of proteasome inhibition in multiple myeloma. Br J Haematol 2017; 178: 547-560.
[67] Siegel D, Martin T, Nooka A, Harvey RD, Vij R, Niesvizky R, Badros AZ, Jagannath S, McCulloch L, Rajangam K and Lonial S. Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies. Haematologica 2013; 98: 1753-1761.
[68] Jouni H, Aubry MC, Lacy MQ, Vincent Rajkumar S, Kumar SK, Frye RL and Herrmann J. Ixazomib cardiotoxicity: a possible class effect of proteasome inhibitors. Am J Hematol 2017; 92: 220-221.
[69] Meseeha MG, Kolade VO and Attia MN. Partially reversible bortezomib-induced cardiotoxicity: an unusual cause of acute cardiomyopathy. J Community Hosp Intern Med Perspect 2015; 5: 28982.
[70] Fradley MG, Groarke JD, Laubach J, Alsina M, Lenihan DJ, Cornell RF, Maglio M, Shain KH, Richardson PG and Moslehi J. Recurrent cardiotoxicity potentiated by the interaction of proteasome inhibitor and immunomodulatory

therapy for the treatment of multiple myeloma. Br J Haematol 2018; 180: 271-275.
[71] Sermer D and Brentjens R. CAR T-cell therapy: full speed ahead. Hematol Oncol 2019; 37 Suppl 1: 95-100.
[72] Martinez M and Moon EK. CAR T cells for solid tumors: new strategies for finding, infiltrating, and surviving in the tumor microenvironment. Front Immunol 2019; 10: 128.
[73] Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, Kochanek M, Böll B and von Bergwelt-Baildon MS. Cytokine release syndrome. J Immunother Cancer 2018; 6: 56.
[74] Penack O and Koenecke C. Complications after CD19+ CAR T-cell therapy. Cancers (Basel) 2020; 12: 3445.
[75] Alvi RM, Frigault MJ, Fradley MG, Jain MD, Mahmood SS, Awadalla M, Lee DH, Zlotoff DA, Zhang L, Drobni ZD, Hassan MZO, Bassily E, Rhea I, Ismail-Khan R, Mulligan CP, Banerji D, Lazaryan A, Shah BD, Rokicki A, Raje N, Chavez JC, Abramson J, Locke FL and Neilan TG. Cardiovascular events among adults treated with chimeric antigen receptor T-cells (CAR-T). J Am Coll Cardiol 2019; 74: 3099-3108.
[76] Shalabi H, Sachdev V, Kulshreshtha A, Cohen JW, Yates B, Rosing DR, Sidenko S, Delbrook C, Mackall C, Wiley B, Lee DW and Shah NN. Impact of cytokine release syndrome on cardiac function following CD19 CAR-T cell therapy in children and young adults with hematological malignancies. J Immunother Cancer 2020; 8: e001159.
[77] Le RQ, Li L, Yuan W, Shord SS, Nie L, Habtemariam BA, Przepiorka D, Farrell AT and Pazdur R. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. Oncologist 2018; 23: 943-947.
[78] Ganatra S, Carver JR, Hayek SS, Ky B, Leja MJ, Lenihan DJ, Lenneman C, Mousavi N, Park JH, Perales MA, Ryan TD, Scherrer-Crosbie M, Steingart RM, Yang EH, Zaha V, Barac A and Liu JE. Chimeric antigen receptor T-cell therapy for cancer and heart: JACC council perspectives. J Am Coll Cardiol 2019; 74: 3153-3163.
[79] Duran JM, Makarewich CA, Trappanese D, Gross P, Husain S, Dunn J, Lal H, Sharp TE, Starosta T, Vagnozzi RJ, Berretta RM, Barbe M, Yu D, Gao E, Kubo H, Force T and Houser SR. Sorafenib cardiotoxicity increases mortality after myocardial infarction. Circ Res 2014; 114: 1700-1712.
[80] Ghosh AK, Chen DH, Guha A, Mackenzie S, Walker JM and Roddie C. CAR T cell therapy-related cardiovascular outcomes and management: systemic disease or direct cardiotoxicity? JACC CardioOncol 2020; 2: 97-109.
[81] Dutcher JP, Schwartzentruber DJ, Kaufman HL, Agarwala SS, Tarhini AA, Lowder JN and Atkins MB. High dose interleukin-2 (aldesleukin) - expert consensus on best management practices-2014. J Immunother Cancer 2014; 2: 26.