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Update on cardio-oncology: Novel cancer therapeutics and associated cardiotoxicities☆,☆☆,☆☆☆

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ABSTRACT

There have been significant advances in the field of oncology leading to improved survival as a result of novel targeted and immunotherapies. Despite these improved outcomes, there is increased recognition of cardiotoxicities associated with these therapies that can lead to significant morbidity and mortality. As such, the field of cardio-oncology has seen significant growth over the last several years. In this review, we discuss recent advances in the field of cardio-oncology and provide a detailed discussion of the cardiovascular complications associated with novel cancer therapeutics including tyrosine kinase inhibitors, proteasome inhibitors, histone deacetylase inhibitors, CDK4/6 inhibitors and immunotherapies.

Introduction

Over the last decade, there have been substantial advances in our understanding of cancer biology which has led to the development of novel classes of therapeutics to treat various malignancies. In the last several years, approximately 60 novel oncology drugs have been approved by the Food and Drug Administration (FDA) [1] leading to significantly improved outcomes. As such, the number of cancer survivors continues to increase at a rapid rate [2]. Despite their oncologic benefit, there is increasing recognition of treatment related cardiovascular (CV) toxicity, and exposure to some of therapies can have an additive effects to traditional CV risk factors, leading to increased long term CV dysfunction. While there has been significant focus on left ventricular ejection fraction (LVEF) reduction and the development of heart failure (HF), cardiotoxicity is much broader and includes diastolic dysfunction, cardiac conduction abnormalities, arrhythmias, and arterial and venous thrombosis and dysfunction particularly among the newer therapeutics (**Table 1**).

Cardio-oncology is a multidisciplinary specialty aimed at minimizing CV risk and preventing CV disease in cancer patients and survivors and was initially focused on CV dysfunction associated with anthracyclines, a problem which was first described in the 1960s [3]. Anthracyclines are chemotherapeutic agents used to treat multiple solid and liquid tumors [4]. Anthracyclines are derived from *Streptomyces* [5] and their anti-cancer effects are mediated by disrupting DNA and RNA synthesis by intercalating between base pairs [6], inhibiting topoisomerase II DNA repair mechanisms [6], attenuating DNA repair via histone eviction [7], as well as creating iron-mediated free radicals [8]. The cardiotoxic effect is dose dependent – at cumulative doses of $\geq$ 400 mg/m^2, the risk of developing left ventricular dysfunction with doxorubicin is greater than 5% [9]. Other traditional chemotherapeutic drugs including cyclophosphamide, 5-fluorouracil cisplatin and arsenic have also been associated with various cardiotoxicities including heart failure and myocardial ischemia, bradycardia and QT prolongation.

There was renewed interest in the field of cardio-oncology with the introduction of the breast cancer drug trastuzumab. Trastuzumab targets the HER2/neu receptor (also known as ErbB2) which is overexpressed in approximately 20% of all human breast cancers. Trastuzumab blocks heterodimerization of ErbB2 and ErbB3, thereby affecting intracellular signaling leading to the activation of apoptotic pathways and cell death. Interestingly, trastuzumab can also affect heterodimerization of ErbB2 and ErbB4 on cardiac myocytes which impacts neuregulin biding to these receptors and leads to contractile dysfunction [10]. Though trastuzumab related cardiac dysfunction was traditionally thought to be reversible, more recent data suggests possible long term cardiotoxicity related to fibrosis and the activation of apoptotic pathways [11,12]. Renal dysfunction [13], excess alcohol consumption

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Table 1
Common cardiovascular toxicities of novel cancer therapeutics.

Toxicity
Cardiac Dysfunction
Cardiomyopathy
Myocarditis
Arrhythmias
QT prolongation
Bradycardia or Heart Block
Atrial arrhythmias
Ventricular arrhythmias or sudden death
Vascular Disease
Ischemic Vascular Events
Venous thromboembolism
Pulmonary Hypertension
Hypertension
Metabolic Disorders
Hyperlipidemia
Impaired Glucose Tolerance
Pericardial disease

[14], systemic hypertension, prior anthracycline treatment, and a history of coronary artery disease [15] have been reported as additional risk factors for the development of trastuzumab induced LV dysfunction.

As a result of the rapid evolution of cancer treatments and the growing number of cancer survivors, there has been a substantial increase in the number of dedicated academic and community-based cardio-oncology programs both domestically and internationally in the last decade. It is imperative, however, that practitioners possess refined knowledge of the cardiotoxicities associated with both traditional as well as novel cancer treatments including tyrosine kinase inhibitors (TKIs), proteasome inhibitors and immunotherapies in order to provide optimal CV care to the cancer patient while minimizing disruption of potentially life-saving treatments. As such, this review will focus on the cardiotoxicities of these novel cancer therapeutics (**Table 2**).

Cardiotoxicities of tyrosine kinase inhibitors

It is now recognized that abnormal intracellular signaling is one mechanism responsible for the unregulated growth and survival of cancer cells. In many cases, this is a result of mutated and/or overexpressed protein kinases (particularly tyrosine kinases) [16]. As such, tyrosine kinase inhibitors are a class of therapeutics that target these abnormal signaling pathways and have led to dramatically improved outcomes in the management of various cancers [17,18]. Despite their significant oncologic benefits, both receptor and non-receptor TKIs are associated with various cardiotoxicities.

Vascular toxicities

Vascular toxicities including hypertension, ischemic heart disease, cerebrovascular disease, and peripheral arterial disease have been associated with various TKIs.

Hypertension is a common side effect of many TKIs, particularly those that target the VEGF receptor including sunitinib and ponatinib (**Table 2**) [19–21]. Mechanisms of arterial hypertension include both functional abnormalities (inactivation of endothelial nitric oxide synthase and production of vasoconstrictors such as endothelin-1) and anatomic abnormalities (capillary rarefaction due to the loss of pericytes from PDGFR inhibition and inhibition of angiogenesis) which can be compounded by concomitant renal dysfunction [22,23]. Interesting, hypertension may be a marker of drug efficacy with an overall survival benefit seen in patients that exhibit a hypertensive response [24]. If hypertension is confirmed, ACE inhibitors and angiotensin receptor blockers are first line treatments with data suggesting a mortality benefit with these agents [25]. Dihydropyridine calcium channel blockers, particularly amlodipine [26,27] can also be considered, however non-dihydropyridine calcium channel blockers should be avoided given their effects on the CYP3A4 system [25]. Ongoing studies are evaluating the utility of nitric oxide donating medications [28] and endothelin antagonists in controlling VEGF-induced hypertension [29].

Nilotinib is a second generation TKI which was approved as first line therapy for the treatment of chronic myeloid leukemia (CML) based on results from the ENESTnd trial [30] demonstrating improved 12-month major molecular response rates compared to imatinib. In this study, serial echocardiography was performed and there was no evidence of LV dysfunction or heart failure, however nilotinib treated patients did demonstrate higher rates of hyperglycemia and hyperlipidemia. With these metabolic abnormalities in the background, there were increasing reports of serious vascular events in patients treated with nilotinib [31–34]. The 6-year follow up safety data from ENESTnd confirmed these observations with rates of cardiovascular, cerebrovascular and peripheral arterial events occurring in approximately 10% of patients treated with nilotinib 300 mg twice daily [35]. There appears to be a predilection for arterial beds with no significant adverse venous events. Postulated mechanisms for these vascular toxicities include accelerated atherosclerosis [36], endothelial dysfunction and/or higher pro-thrombotic state [37].

Ponatinib is a 3rd generation TKI used primarily to treat CML. It was initially withdrawn from the market due to increased rates of stroke but regained FDA approval as 3rd line therapy in patients with refractory disease, or in patients with the T315I mutation which renders other TKIs ineffective [38]. Follow up safety data from the PACE trial demonstrated rates of ischemic cardiovascular, cerebrovascular and peripheral arterial events at 16%, 13% and 14% respectively [39]. Though there appears to be a predilection towards arterial beds (serious arterial events at 31%), serious adverse venous events are also seen with ponatinib, with rates reported at 3–6% [39,40]. Patients with traditional risk factors for CV disease including baseline hypertension and diabetes were at increased risk for these adverse vascular events [39,41]. The exact pathophysiologic mechanism of ponatinib associated vascular events remains unclear and may be distinct from nilotinib [42].

Dasatinib is a second generation TKI used in CML. It has been associated with several pulmonary toxicities including an increased risk of pleural effusions which can be seen in up to 30–35% of patients within 2 years of treatment [43]. Despite this finding, treatment discontinuation is rarely necessary [44]. Dasatinib has also been associated with pulmonary hypertension with an incidence as high as 5% in the DASISION trial [45] and 2.4% in the 7-year follow-up of the CA180-034 trial [44]. This side effect is mostly reversible [46] however when present, it does require permanent discontinuation of therapy [47]. While significant attention has been paid to dasatinib-associated pulmonary toxicities, there increasing evidence that vascular complications may also occur. Five-year follow up data from the DASISION trial reported a higher rate of arterial ischemic events with dasatinib (5%) compared to imatinib (2%) [45]. A recently published meta-analysis also demonstrated an increased risk of vascular events with dasatinib (OR 3.86; 95% CI 1.33–11.18) [48].

Arrhythmias

There has been an increased recognition of atrial and ventricular arrhythmias as well as QT prolongation associated with use of tyrosine kinase inhibitors [16,49–53]. Atrial fibrillation has been the most reported arrhythmic complication of these agents. Ibrutinib, an inhibitor of the Bruton's tyrosine kinase protein

Table 2
Cardiotoxicities of recently approved cancer therapeutics.

Agent, Class	Cancer/Cancers approved for	Side effects	Reference
Receptor Tyrosine Kinase inhibitor (TKI)			
Afatinib (epidermal growth factor receptor (EGFR) inhibitor)	Non-small cell lung cancer (NSCLC)	No cardiovascular side effects	[156]
Erlotinib (EGFR inhibitor)	EGFR positive NSCLC	Heart failure (HF)	[157]
Neratinib (dual Her2 and EGFR inhibitor)	HER2 + breast cancer	Ischemic vascular events (IVE), QT prolongation (QTP), HF	[158,159]
Osimertinib (EGFR inhibitor)	EGFR positive (NSCLC)	QTP	[136,160]
Small molecule TKI			
Acalabrutinib (second generation BTK inhibitor)	mantle cell lymphoma (MCL), Chronic lymphocytic leukemia (CLL)	IVE	[161]
Alectinib (anaplastic lymphoma kinase (ALK) inhibitor)	ALK-positive NSCLC	QTP, pulmonary embolism (PE)	[162]
Bosutinib (BCR-Abl inhibitor)	Chronic myelogenous leukemia (CML)	Hypertension (HTN), IVE, QTP, atrial fibrillation (AF)	[163]
Brigatinib (ALK and EGFR inhibitor)	Metastatic ALK-positive NSCLC	IVE, PE	[135]
Cabozantinib (c-Met, VEGFR2*, AXL and RET inhibitor)	advanced renal cell carcinoma (RCC)	HTN, Hyperlipidemia (HLD)	[164,165]
Ceritinib (ALK inhibitor)	ALK-positive NSCLC	IVE, sinus bradycardia (SB)	[166]
Crizotinib (ALK and ROS1 inhibitor)	Metastatic ALK-positive NSCLC	SB	[167]
Dabrafenib (BRAF inhibitor)	Melanoma, NSCLC with BRAF V600E mutation	HTN, HF, PE, QTP	[168-171]
Dasatinib (BCR/Abl*, Src, c-Kit, ephrin receptor inhibitor)	CML	Pleural effusion, pulmonary hypertension, IVE, QTP	[172]
Ibrutinib (first generation BTK inhibitor)	chronic graft versus host disease, CLL, MCL, Waldenström's Macroglobulinemia	AF, VT, VF, sudden cardiac death (SCD)	[55]
Lenvatinib (VEGFR1-3 inhibitor)	advanced RCC	HLD, IVE, intracranial hemorrhage (ICH)	[173]
Nilotinib (BCR-ABL*, KIT, LCK, EPHA3, EPHA8, DDR1, DDR2, PDGFRB, MAPK11 and ZAK inhibitor)	CML	HTN, IVE, QTP, HLD, hyperglycemia	[35,174,175]
Ponatinib (BCR-Abl inhibitor)	CML, Philadelphia chromosome + acute lymphoblastic leukemia	HTN, HF, IVE, PE	[38,45,163]
Regorafenib (VEGFR2-TIE2 tyrosine kinase inhibitor)	hepatocellular carcinoma (HCC)	HTN, IVE, cardiac death	[176–179]
Sunitinib (PDGF and VEGF inhibitor)	RCC Gastrointestinal Stromal Tumor	HTN	[180,181]
Trametinib (MEK inhibitor)	Melanoma, NSCLC with BRAF V600E mutation	HTN, HF, PE, QTP, SCD	[168,170,172]
Vemurafenib (BRAF inhibitor)	Melanoma, Erdheim-Chester Disease	QTP, pericarditis	[182–185]
Protein Kinase Inhibitor			
Midostaurin (FMS-like tyrosine kinase 3 receptor (FLT3) inhibitor)	FLT3 + acute myeloid leukemia (AML)	No cardiovascular events	[186]
poly (ADP-ribose) polymerase (PARP) inhibitor			
Olaparib	HER2 negative breast cancer Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer	Pericarditis, PE and syncope	[187–189]
Rucaparib	BRCA positive advanced ovarian cancer	HTN, QTP, HLD	[190]
Niraparib	Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer	HTN	[191]
Cyclin Dependent Kinase (CDK) inhibitor			
Abemaciclib (CDK4/CDK6 inhibitor)	Hormone Receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer	PE	[192,193]
Palbociclib (CDK4/CDK6 inhibitor)	HR-positive, HER2- negative advanced or metastatic breast cancer	PE, HTN, AF	[110,194]
Ribociclib (CDK4/CDK6 inhibitor)	HR-positive, HER2-negative advanced or metastatic breast cancer	QTP	[195,196]
Histone DeACytylase (HDAC) inhibitor			
Panabinostat	Multiple myeloma	No reported cardiac side effects	[197]
Romidepsin	Cutaneous T-cell lymphoma (TCL)	QTP	[198,199]
Belinostat	Peripheral TCL	QTP	[200]
Mitochondrial enzyme inhibitor			
Enasidenib (isocitrate dehydrogenase-2 inhibitor)	Relapsed or refractory AML with an isocitrate dehydrogenase-2 (IDH2) mutation	No reported cardiac side effect	[201]
PI3K inhibitor			
Copanlisib (PI3K-α/PI3K-δ inhibitor)	Relapsed follicular lymphoma	HTN	[202,203]
HER2 inhibitor			
Pertuzumab	HER-2 positive breast cancer in	HF, cardiac death	[204]
Checkpoint Inhibitor			
Atezolizumab (PD-L1 inhibitor)	Metastatic NSCLC; advanced urothelial carcinoma	Myocarditis, HF, HTN, PE, AF, heart block, SCD	[142-144,205]
Avelumab (programmed cell-ligand death (PD-L1) inhibitor)	Advanced urothelial carcinoma; metastatic Merkel cell carcinoma	Myocarditis, HF, AF, heart block, SCD	[132,133]
Durvalumab (PD-L1 inhibitor)	Advanced urothelial carcinoma, NSCLC	Myocarditis, HF, HTN, PE, AF, heart block, SCD	[134,206]

(*continued on next page*)

Table 2 (*continued*)

Agent, Class	Cancer/Cancers approved for	Side effects	Reference
Nivolumab (programmed cell death (PD)−1 inhibitor)	Stage 3 or 4 Melanoma; HCC; metastatic colorectal cancer; advanced urothelial carcinoma; recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN); post hematopoietic stem cell transplant relapsed Hodgkin's lymphoma (HL); NSCLC	Myocarditis, HF, AF, heart block, SCD	[113,137,138,145, 207–210]
Pembrolizumab (PD-1 inhibitor)	Metastatic, gastric or gastroesophageal junction adenocarcinoma; advanced colorectal cancer; advanced urothelial carcinoma; metastatic NSCLC; refractory HL; metastatic SCCHN	Myocarditis, HF, AF, heart block	[114,115, 117–131, 139–141,211]
Antibody (Ab)			
Blinatumomab (CD3 and CD-19 MoAb)	Relapsed or refractory B-cell precursor ALL	AF, IVE, HF	[212,213]
Brentuximab vedotin (CD- 30 whole Ab)	Primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides, HL	HLD, PE	[214,215]
Daratumumab (CD- 38 whole Ab)	Multiple myeloma who have received at least one prior therapy	No direct cardiac side effects	[216]
Gemtuzumab Ozogamicin (CD-33 MoAb)	CD33-positive AML	No direct cardiac side effects	[217]
Inotuzumab ozogamicin (CD-22 MoAb)	Relapsed or refractory B-cell precursor ALL	No direct cardiac side effects	[218]
Obinutuzumab (CD-20 Monoclonal Ab (MoAb))	Stage II-IV follicular lymphoma (FL)	AF, IVE, HF, PE	[219,220]
Ofatumumab (CD-20 MoAb)	CLL	HTN	[221]
Olaratumab (PDGFR whole Ab)	soft tissue sarcoma	HF	[222]
Chimeric antigen receptor or CAR-T			
Axicabtagene Ciloleucel	Relapsed or refractory large B-cell lymphoma	AF, HF	[223]
Tisagenlecleucel	B-cell precursor acute lymphoblastic leukemia (ALL)	None specific to the medication	[224]
Taxane			
Cabazitaxel	Metastatic castration-resistant prostate cancer	No CV side effects reported	[225]
Immunomodulator			
Lenalidomide	Multiple myeloma	IVE; Venous thromboembolic events; Conduction abnormalities	[226,227]
Pomalidomide	Multiple myeloma	Venous thromboembolic events	[228]
Proteasome Inhibitor			
Carfilzomib	Multiple myeloma	HTN, HF, arrhythmias	[79]
Ixazomib	Multiple myeloma	No direct cardiac side effects	[95,229,230]
Androgen Synthesis Inhibitor			
Abiraterone acetate (steroidal CYP17A1 inhibitor)	Metastatic high-risk castration-sensitive prostate cancer	HTN, AF, IVE, HF	[231]
Small Molecule Proteins			
Ventoclax (anti-apoptotic B-cell lymphoma-2 (Bcl-2 protein)	CLL	AF, ICH, HTN	[232]
Immunosuppressant			
Everolimus (mTOR inhibitor)	Well-differentiated non-functional, neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin	HTN, HLD	[233]
Microtubule Inhibitor (inhibits mitosis)			
Eribulin	Unresectable or metastatic liposarcoma; metastatic breast cancer	No CV side effects reported	[234,235]

(BTK), is approved for treatment of mantle cell lymphoma (MCL) [54], chronic lymphocytic leukemia (CLL) [55], Waldenstrom's Macroglobulinemia [56] and chronic graft-versus-host disease [55]. Multiple studies as well as meta-analyses have reported a strong link between ibrutinib and the development of AF and other atrial arrhythmias [55–58]. A recent publication evaluating patients in four large randomized controlled studies reported AF incidence of 10.4% (95% CI: 8.4, 12.9) at 36-month follow-up [57]. The risk of AF with ibrutinib appears to increase with ongoing therapy. One possible mechanism by which this agent can cause AF is due to reduced phosphoinositide 3-kinase (PI3K)-Akt activity as a result of BTK and tec protein tyrosine kinase inhibition [51,59,60].

It should be noted that there is an increased risk of clinically significant bleeding associated with ibrutinib which complicates the management of AF in these patients [61,62]. Serious bleeding complications are especially common in patients who were treated with vitamin K antagonists with up to 6% of patients experiencing grade $\geq$ 3 bleeding events and 2% reporting subdural hematomas in one clinical trial [63]. As such, it is recommended to avoid treating patients on ibrutinib with warfarin [64]. Currently, data evaluating the use of direct-acting oral anticoagulants (DOACs) in the setting of ibrutinib-associated AF is lacking, although several phase III trials have demonstrated fewer bleeding events with these agents in comparison to warfarin in the general population [62,65].

Ibrutinib has also been associated with the development of ventricular arrhythmias. The HELIOS trial reported 7 instances of grade $\geq$3 ventricular arrhythmias, cardiac arrests, and sudden deaths in the ibrutinib-containing arm versus 0 in the placebo-containing arm [66]. Another recent study evaluating ibrutinib-treated patients in the FDA Adverse Event Reporting System (FAERS) documented 7 instances of ventricular tachycardia (VT) and ventricular fibrillation (VF) as well as 6 sudden deaths [53].

Sunitinib is a TKI used primarily to treat renal cell carcinoma and gastrointestinal stromal tumors (GIST). While it has been reported to cause AF, the exact incidence is unknown and many of these arrhythmic events occur in the setting of heart failure and LV dysfunction which has been reported at rates of up to 15% in the literature [52,67,68]. Sorafenib, another TKI commonly used in the treatment of renal cell carcinoma, is also associated with AF with an incidence of 5.1% [69,70].

QT prolongation is a common side effect of many TKIs including dasatinib and nilotinib [49,71]. QTc prolongation greater than 30 ms has been reported in up to 26% of patients treated with nilotinib leading to a Black Box Warning for QT prolongation and sudden cardiac death (SCD) [72–75]. A similar Black Box Warning exists for vandetanib, a VEGF inhibitor used primarily to treat medullary thyroid cancer [73,74]. Sunitinib has also been associated with dose-dependent QTc prolongation with average increase in the QTc of about 15.4 ms (90% CI: 8.4–22.4 ms) [76].

While less common, brady-arrhythmias are observed with several TKIs. Crizotinib and ceritinib have been associated with sinus bradycardia which is usually asymptomatic and rarely requires therapy interruption. One study of patients undergoing therapy with crizotinib reported development of bradycardia below 50 beats per minute in about 31% of patients [77].

Cardiotoxicities of proteasome inhibitors and immunomodulatory drugs

Bortezomib, carfilzomib and ixazomib are proteasome inhibitors (PI) and thalidomide, lenalidomide and pomalidomide are immunomodulatory drugs (IMiD) used primarily the treatment of multiple myeloma and AL amyloidosis.

The proteasome is an intracellular structure that degrades abnormal proteins. Proteasome inhibitors affect the functioning of this structure leading to the accumulation of toxins and ultimately cellular apoptosis [78]. There appears to be a clear cardiotoxic signal associated with the second generation irreversible PI, carfilzomib. In a pooled analysis of 4 phase II single-agent carfilzomib trials, cardiotoxicities were observed in 22% of patients. These toxicities included hypertension (14.3%), arrhythmias (13.3%) and heart failure (7.2%) [79]. In the recently released phase III ENDEAVOR trial comparing carfilzomib to bortezomib, rates of heart failure (10.8% vs. 4.1%) and hypertension (20.3% vs. 8.1%) were significantly increased in the carfilzomib group [80]. In contrast, while there are reports in the literature of cardiotoxicities associated with bortezomib including heart failure, ischemic heart disease and complete AV block, a retrospective pooled analysis of phase II and phase III trials failed to demonstrate an increased risk of cardiovascular complications in patients exposed to bortezomib [81]. Similarly, ixazomib, the most recently approved PI has not shown clear evidence of cardiotoxicity. Given these data, PI-induced cardiotoxicity does not appear to be a class-related effect [82].

The primary cardiovascular toxicities associated with IMiDs are arterial and venous thromboembolism [83]. These toxicities are observed with all IMiDs though rates reported in the literature vary widely, ranging from less than 1% up to 25% [83]. Arterial thrombosis is of particular concern with lenalidomide – analysis of two multicenter trials demonstrated increased rates of myocardial infarction (1.98%) and cerebrovascular events (3.4%) leading the FDA to issue a Black Box warning for arterial thrombotic events with lenalidomide [84]. In addition, both thalidomide and lenalidomide are associated with development of arrhythmias including AF and sinus bradycardia [85,86].

The mechanism of PI-induced cardiotoxicity remains unclear however PIs are known to impair nitric oxide production [87] and homeostasis as well as having adverse effect on vascular smooth muscle and plaque stability [88]. In addition, rat data suggests PIs can induced mitochondrial dysfunction leading to decreased ATP synthesis and ultimately decreased myocardial contractility [89] and in a porcine model, chronic proteasome inhibition contributes to coronary atherosclerosis [82]. While the exact mechanism of IMiD associated thrombosis remains uncertain, it is postulated that dysregulation of endothelial thrombotic pathways may play an important role in the development of this toxicity [90]. Moreover, recent data suggests IMiD binding to cereblon protein and its effects on the transcription factors IKZF1 and IKZF3 may be central to the development of these vascular events [91]. Finally, it should be recognized that in practice, PIs and IMiDs are frequently co-administered along with steroids which may potentiate the development of CV toxicities [92–95]. CV risk factor management including strict blood pressure control along with the development of thromboprophylaxis protocols may help minimize the likelihood of developing these complications [96–101].

Cardiotoxicities of HDAC inhibitors

Histone deacetylase (HDAC) inhibitors are a group of targeted pharmaceuticals that modulate the posttranscriptional activity of proteins by inactivating histone deacetylase enzymes thereby affecting normal cell cycle progression and leading to apoptosis [102]. The majority of HDAC inhibitors are approved to treat cutaneous or peripheral T-cell lymphoma with the exception of panobinostat which is used in the treatment of multiple myeloma. Several HDAC inhibitors have demonstrated QT interval prolongation; for example the mean QT interval change is 14 ms in patients treated with romidepsin [103]. Sudden death from TdP has been reported in some of the early clinical trials however detailed analyses of these cases revealed most patients had baseline cardiac comorbidities thereby predisposing them to these outcomes [104,105]. Strategies to minimize QT interval changes in patients receiving HDAC inhibitors include electrolyte monitoring and repletion and minimizing the use of concomitant QT prolonging medications [105]. QTc prolongation is thought to be mediated in part by transcriptional changes of genes required for HERG-K+ ion channel trafficking and localization to the sarcolemma [106].

Cardiotoxicities of CDK4/6 inhibitors

Cyclin Dependent Kinase (CDK) dysregulation or inhibition of CDK regulating proteins is associated with cancer cell proliferation [107]. CDK 4/6 inhibitors counteract this process and have been shown to be efficacious in the treatment of advanced or metastatic breast cancer with disease progression following endocrine therapy [108]. There are ongoing clinical trials evaluating the utility of these agents for leukemia, melanoma and other solid tumors. The 3 CDK 4/6 inhibitors approved by the FDA are ribociclib, palbociclib and abemaciclib. Significant QT prolongation has only been observed with ribociclib. In the MONALEESA-2 trial, a QTc increase of more than 60 ms from baseline was demonstrated in 2.7% of the patients in the ribociclib group, and 3.3% of the patients had an average QTc interval of more than 480 ms [108]. Although there are no reported cases of torsades de pointes with any CDK4/6 inhibitors, routine EKG monitoring for QT prolongation is recommended along with avoiding electrolyte imbalances and minimizing the use of concomitant QT prolonging medications. [109]. Additionally, thromboembolic events have been reported with palbociclib and ribociclib with rates of 1.8% and 5% respectively in the various clinical trials [108,110–112].

Cardiotoxicities of immunotherapies

Checkpoint inhibitors

Immunotherapies have revolutionized the management of various cancers with otherwise dismal prognoses. Monoclonal antibodies targeting immune check points namely - cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death 1 antigen (PD-1) and its ligand (PD-L1) have become an increasingly utilized group of immunotherapies for many advanced malignancies [113–145]. There is increasing data suggesting checkpoint inhibitors are associated with CV toxicities, particularly

myocarditis. PD1 is robustly expressed in the myocardium and mouse models deficient in both PD1 and CTLA demonstrate LV dilation, systolic dysfunction and T-cell mediated inflammatory infiltrates [146–148]. A recent study from Moslehi et al [149] using Vigibase [150], a World Health Organization (WHO) drug monitoring database, reported 101 cases of checkpoint inhibitor myocarditis with median onset of 27 days. The majority of patients (57%) received anti-PD-1 monotherapy, and multiple other immune-related adverse events including myositis occur simultaneously in 42% of patients. In this cohort, mortality was 46% with a higher frequency observed with combination checkpoint blockade. Mahmood et al [151] reported a prevalence of myocarditis of 1.14% with a median time to onset of 34 days. Multivariate analysis demonstrated myocarditis was most likely to occur in the setting of combination checkpoint blockade and in patients with diabetes. Additionally, major adverse cardiac events (MACE) were observed in 46%, and 38% of MACE occurred in the setting of a normal ejection fraction. Moreover, there was a 4-fold increased likelihood of MACE in patients with troponin T of ≥ 1.5 ng/ml. Higher steroid dosing was associated with lower CV event rates. In addition, arrhythmias including sinus tachycardia, atrial fibrillation, complete heart block and SCD have been reported possibly as a result of underlying myocarditis [152,153].

CAR-T cell therapy

Chimeric antigen receptor therapy (CAR-T therapy) is a novel immunotherapy modality where T-cells are genetically modified to target tumors. CAR-T cell therapy has been efficacious in the treatment of various hematological malignancies; however, cardiotoxcities have been described generally as a consequence of cytokine release syndrome (CRS). This is an acute inflammatory process which may include tachycardia, hypotension/shock, and cardiac dysfunction as well as high fevers, renal and hepatic dysfunction, and disseminated intravascular coagulation. There is also an increased risk of arrhythmias including SVT and atrial fibrillation. One recently published study evaluating CV complications in 93 children treated with CAR-T therapy for leukemia reported cardiac events in 36% of the patients at a mean onset of 4.8 days after infusions. Of this group, 35% had evidence of systolic or diastolic dysfunction on echocardiography and 18% required milrinone for inotropic support [154]. Despite this, only 2% had persistent dysfunction at 6 months [154]. As CAR-T therapy is used more frequently, there may be increased recognition and reporting of cardiotoxicities particularly in the adult population.

Conclusions and future direction

Due to significant advances in the treatment of various cancers, the number of cancer survivors is increasing at a rapid pace. Cardiovascular disease is the leading cause of non-malignancy related death in cancer survivors which at times may be a result of cardiotoxicities associated with their cancer treatments [155]. As such, further research is necessary to better understand the mechanisms of action of these therapies and how they affect the CV system including tyrosine kinase inhibitors, proteasome inhibitors and novel cancer immunotherapies. Moreover, it is important to improve our identification of those at highest risk for development of cardiotoxicities prior to treatment through establishment of guideline-directed screening recommendations. The collaboration between cardiologists and oncologists in the management of treatment-related cardiotoxicities is essential in order for patients to continue receiving optimal cancer care while minimizing both short- and long-term CV risk.

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