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STATE OF THE ART REVIEW
Cardio-oncology

Use of new and emerging cancer drugs: what the cardiologist needs to know

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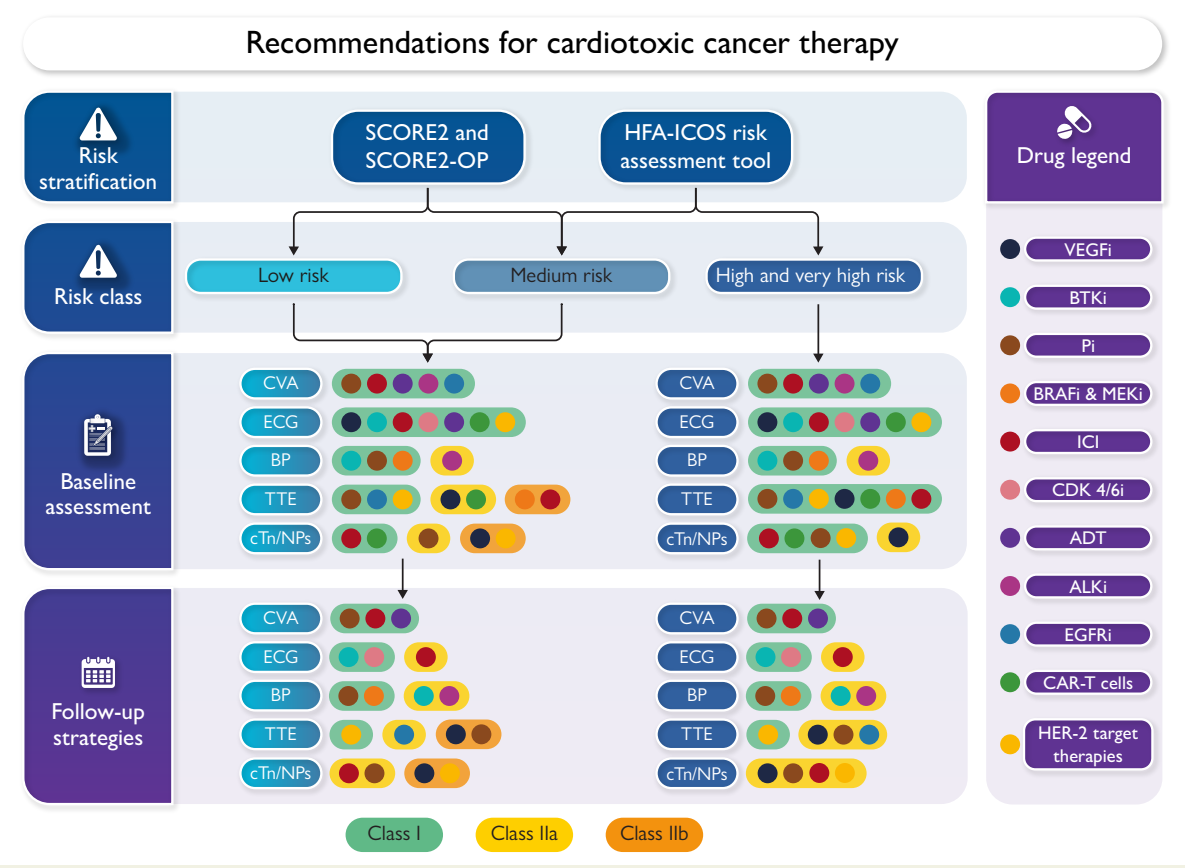
Graphical Abstract



Main recommendations concerning risk stratification, assessment at baseline, and follow-up of patients undergoing potentially cardiotoxic cancer therapy. ADT, androgen deprivation therapy; ALKi, anaplastic lymphoma kinase inhibitor; BP, blood pressure; BRAFi, v-raf murine sarcoma viral

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oncogene homologue B1 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T; CDK 4/6i, cycle-independent kinase 4/6 inhibitor; cTn, cardiac troponin; CV, cardiovascular; CVA, CV assessment; ECG, electrocardiogram; EGFRi, epidermal growth factor receptor inhibitor; HER-2, human epidermal growth factor receptor 2; HFA-ICOS, Heart Failure Association-International Cardio-Oncology Society; ICI, immune checkpoint inhibitor; MEKi, mitogen-activated protein kinase inhibitor; NP, natriuretic peptide; PI, proteasome inhibitor; TTE, transthoracic echocardiography; VEGFi, vascular endothelial growth factor inhibitor. Created with Biorender.com.

Abstract

The last decade has witnessed a paradigm shift in cancer therapy, from non-specific cytotoxic chemotherapies to agents targeting specific molecular mechanisms. Nonetheless, cardiovascular toxicity of cancer therapies remains an important concern. This is particularly relevant given the significant improvement in survival of solid and haematological cancers achieved in the last decades. Cardio-oncology is a subspecialty of medicine focusing on the identification and prevention of cancer therapy–related cardiovascular toxicity (CTR-CVT). This review will examine the new definition of CTR-CVT and guiding principles for baseline cardiovascular assessment and risk stratification before cancer therapy, providing take-home messages for non-specialized cardiologists.

Keywords Cardiotoxicity • New cancer drugs • Cardio-oncology • Target therapy • Cardiovascular disease • Imaging

Introduction

During the last decade, there has been a paradigm shift in the approach to cancer therapy, from non-specific cytotoxic chemotherapies (e.g. anthracyclines) to agents targeting specific molecular targets such as monoclonal antibodies, immune checkpoint inhibitors (ICIs), and antibody–drug conjugates. These therapies have led to better clinical outcomes for patients with both solid and haematological malignancies; however, they have been associated with a wide spectrum of toxicities, including cardiovascular (CV) toxicity. The introduction of new anti-cancer drugs poses many challenges to the clinician including identification and predictability (stratification at baseline) of cancer therapy–related cardiovascular toxicity (CTR-CVT). Clinicians may not be familiar with the management of patients who develop CTR-CVT.

Although cardio-oncology clinics and programmes have emerged globally, many patients with cancer do not have access to this specialized care, and therefore general cardiologists should have a basic understanding of how to approach patients with cancer who are at risk of CTR-CVT.

Considering the most recent European Society of Cardiology (ESC) cardiology guidelines published in 2022, this paper will provide the main concepts of early detection, prevention, and treatment of CTR-CVT. The CTR-CVT of modern cancer therapies will be described, and recommendations made on when it would be appropriate to refer to providers with expertise in Cardio-Oncology.

Definitions of cancer therapy–related cardiovascular toxicity

Several definitions of CTR-CVT have been used in clinical studies, which make the comparison between single studies challenging. An international consensus document proposed a standardized definition of CTR-CVT.[1,2] The term 'cancer therapy–related cardiac dysfunction' (CTRCD) has been suggested since it encompasses the wide range of potential manifestations and the aetiological connection with cancer therapies like chemotherapy, targeted therapies, immunological therapies, and radiation therapy.

Baseline risk stratification: general principles

The severity, duration, and type of manifestation of CTR-CVT vary by the type of malignancy and cancer treatment. The risk of CTR-CVT depends on the individual CV risk before cancer therapy and changes over time. This risk should be considered in terms of the likelihood and severity of a complication.[3,4] For instance, a patient maybe at high risk of experiencing CTR-CVT, but if the event is minor, cancer therapy should continue. In contrast, a patient with a low risk of CTR-CVT may nevertheless be at high risk for serious complications, such as a considerable drop in left ventricular ejection fraction (LVEF) to <40% following administration of anthracyclines, which may necessitate discontinuing cancer therapy. It is therefore crucial that patients receiving cardiotoxic anticancer therapy are managed by a multi-disciplinary team that includes cardio-oncology staff and oncology partners in order to evaluate a potential permissive cardiotoxicity strategy based on the type of emerging cardiotoxicity, associated symptomatology, and the beneficial costs related to a possible discontinuation or continuation of therapy.[5]

Tools for baseline examination and risk assessment

The baseline CV risk assessment should include a thorough clinical history and physical examination. Patients should be questioned about their cardiac symptoms, and a physical examination should record vital signs and check for any potential undetected CV disease (CVD) symptoms including heart failure (HF), valvular heart disease, and pericardial disease.[6,7] When traditional risk factors for CVD are present, they should be optimally controlled.[8,9] A primary prevention strategy can be considered in patients without previous CVD or CTR-CVT but deemed at high or very high risk.

To improve risk assessment in patients older than 40, the systematic coronary risk evaluation 2 (SCORE2) and systematic coronary risk evaluation 2-older person (SCORE2-OP) are suggested to assess the risk of vascular toxicity, even though these tables are not specific for cancer patients. The SCORE2 and SCORE2-OP algorithms assess the 5- and 10-year risks of fatal and non-fatal CVD and are used for

apparently healthy patients aged <70 and ≥70 years, respectively[1,10] (*Graphical Abstract*).

Patients with known CVD are at high or very high risk of developing a further CV event[11] and need a more thorough clinical assessment of their CVD, its severity, and current and previous treatments. Further investigations may be required depending on the type and severity of CVD. The type, duration, and intensity of cancer treatment, as well as the prognosis and type of cancer, are additional variables that complicate the baseline CV risk evaluation.[8,11,12]

For cancer patients, a small number of CV risk prediction models have been published, most of which have been established for specific cancer patient populations and cannot be easily transferred to or generalized to other types of cancer.[13–18] The HF Association-International Cardio-Oncology Society (HFA-ICOS) developed 'baseline CV risk stratification proformas', which considered seven different classes of anti-cancer drugs and baseline CV risk factors, prior CVD, demographics, lifestyle risk factors, previous cancer therapy, and cardiac biomarkers (when available). Patients are classified (based on a point system) into low risk, intermediate risk, high risk and very high risk of CTR-CVT; risk calculation is performed by assigning a score to each risk factor.[19] The risk of future CTR-CVT for each of the risk groups is as follows: low risk, ≤2%; medium risk, 2%–9%; high risk, 10%–19%; and very high risk ≥20%.[19] While future research is required to validate the HFA-ICOS risk assessment tool (except for the score dedicated to HER2 target therapies, which was validated by Battisti *et al.*[20]) the ESC Cardio-Oncology guideline currently endorses its use before the start of a potential cardiotoxic therapy[1,19] (*Graphical Abstract*).

As part of baseline risk stratification, a 12-lead electrocardiogram (ECG) is recommended before starting cancer treatment, particularly for patients receiving cancer drugs known to prolong the corrected QT (QTc) interval[21–26] (*Graphical Abstract*). Evidence supporting the use of biomarkers for CTR-CVT risk stratification before cancer therapy is limited.[12,19,27,28] Cardiac biomarker measurement, including natriuretic peptides (NPs) [e.g. B-type NP (BNP) or N-terminal pro-BNP (NT-proBNP)] and cardiac troponin (cTn) I or T, help identify patients who may benefit from cardioprotective therapies.[12,27,28] Notably, the finding of increased cTn and BNP values at baseline should not prevent the start of cancer treatment.[10]

Numerous studies have demonstrated the importance of baseline NP measurement or how NP alterations may predict future CTR-CVT.[29,30] Therefore, NP measurement at baseline is recommended in high- and very high-risk patients undergoing treatment with anthracyclines, HER2-targeted therapies, proteasome inhibitors (PIs), ICIs, and chimeric antigen receptor (CAR) T cells inhibitors (Class I).[1] Measurement of NPs is also recommended in low- and moderate-risk patients, although with a lower level of evidence. It is unclear whether pretreatment cTn levels will be predictive of left ventricular dysfunction (LVD) in patients before any treatment or for breast cancer patients treated with trastuzumab without prior anthracyclines. Cardiovascular biomarker monitoring should be used throughout treatment to diagnose CTRCD and to direct potential cardioprotective therapy.[28] The results should be interpreted according to each patient's clinical context because the degree of cTn and NP change is directly related to both the type of cancer therapy the patient is receiving and the patient's comorbidities.

Cardiovascular imaging plays a crucial role both in identifying patients with subclinical CVD and as a tool to detect early and monitor cardiac damage during follow-up.[19,31–33] Transthoracic echocardiography (TTE) is the preferred imaging technique for baseline risk stratification. Transthoracic echocardiography is recommended before initiation of cancer treatment in all patients with cancer at high risk and very high risk of CV toxicity[1] (*Graphical Abstract*). Acquisition of LVEF at baseline preferably by 3D echocardiography is recommended in all patients assessed with TTE before the start of treatment.[30,34] When available, global longitudinal strain (GLS) analysis can be an additive tool to assess left ventricular function.[1] Although several studies have suggested the superiority of GLS over LVEF measurement for follow-up of patients undergoing cardiotoxic therapy, the recent 3-year results of the SUCCOUR study do not support this evidence.[35] Specifically, GLS-based cardioprotective therapy for early detection of CTRCD was not shown to be superior to LVEF-guided therapy. Given the low incidence of significant changes in ejection fraction (EF) and GLS (9% and 5%, respectively) and the overall low likelihood of developing LVD, future studies with a different patient selection strategy are needed to confirm these findings.

In patients with an inadequate acoustic window, CV magnetic resonance (CMR) should be considered.[31,36]

Chest computed tomography (CT) performed for cancer staging may detect coronary calcium, as cancer patients are at increased risk of developing coronary artery disease (CAD). This relationship is explained by the pro-inflammatory state that these patients display,[37,38] risk factors shared with CVD (such as obesity, diabetes, and smoking),[9] and the CV toxicity of cancer treatments.[39]

A thorough evaluation should start with a comprehensive TTE for baseline assessment and to ascertain the severity of the underlying CVD in the secondary prevention setting or in patients with signs or symptoms of pre-existing CVD. If there is a clinical suspicion of CAD, functional imaging studies for myocardial ischaemia should be conducted in symptomatic patients, particularly before using cancer therapies linked with vascular toxicity.[1] In these patients, with a lower range of clinical likelihood of CAD, no prior diagnosis of CAD, and characteristics associated with a high likelihood of high image quality, coronary CT should be considered as first-line examination.[40]

Cardiovascular assessment in patients receiving specific cancer drugs

Vascular endothelial growth factor inhibitors

Suppression of the vascular endothelial growth factor (VEGF) signalling pathway can occur by impairing VEGF–VEGFR2 interaction or by inhibiting downstream intracellular signalling elements.[41,42] Monoclonal antibodies include bevacizumab,[43] targeting VEGFA, and ramucirumab[44] (*Figure 1*; see Supplementary data online, *Table S1*), a humanized antibody directed against VEGFR2. Aflibercept is a decoy receptor for circulating VEGF.[45] Tyrosine kinase inhibitors (TKIs) include 10 approved drugs (apatinib, axitinib, cabozantinib, lenvatinib, nintedanib, pazopanib, regorafinib, sorafenib, sunitinib, and vandetanib), with many more drugs in the pipeline.[46]

Main cardiovascular toxicities

The indications for VEGF inhibitors (VEGFi) include metastatic colorectal cancer, renal cell carcinoma, pancreatic cancer, and thyroid cancer. The most prevalent adverse effect of VEGFi is hypertension, which manifests within hours to days, is dose-dependent, and can be reversed by discontinuing VEGFi.[47] Hypertension manifests in 25%–30% of patients[47,48] and in almost all when multiple VEGFi are combined.[49] Vascular endothelial growth factor inhibitor may also cause cardiac

ischaemia, systolic dysfunction, and arterial thromboembolism, with no significant difference between VEGF ligand inhibitors and small molecule agents.[50] Reduced nitric oxide production and developing endothelial dysfunction promote arterial inflammation, atherosclerosis, and platelet reactivity. Therefore, inhibition of VEGF signalling pathway may have significant functional consequences.[51] Myocardial perfusion and vascular pressure can both be significantly reduced because of coronary vasoconstriction. The integrity of the coronary microcirculation has been shown to be substantially altered by sunitinib, with a pronounced decrease in coronary flow reserve and compromised cardiac function.[52]

Corrected QT prolongation has also been described and is associated with severe arrhythmic events only with vandetanib therapy.[53] Of note, a recent retrospective pharmacovigilance study by Goldman *et al.*[54] analysed a total of 51 836 adverse events related to anti-VEGFR drug administration, showing correlation with the occurrence of pericardial disease (0.3%) and aortic dissection (0.1%).

Available data on the cardiotoxicity of the most recently approved drugs are scarce. Axitinib has been associated with acute aortic events, and there is a report of LVD in a patient treated with axitinib and nivolumab.[55] A retrospective study of 35 patients treated with pazopanib found CV events in 34% of patients.[56]

Recommendations

Baseline CV risk assessment, including a clinical examination, blood pressure (BP) measurement, glycaemic and lipid profiling, and QTc measurement, is recommended.[57] Blood pressure should be managed before initiating VEGFi treatment in hypertensive patients and strictly monitored. Home BP monitoring is advised every day during the first cycle and following each increase in treatment dose and every 2–3 weeks after that.[58–60] A standard TTE is indicated for patients at high risk. Screening for CTR-CVD through clinical examination, echocardiography, and NP measurement is advisable[1,58–60] (Class I, Level C).

Transthoracic echocardiography should be performed every 4 months during the first year of treatment with VEGFi in moderate-risk patients (Class IIb, Level C) and every 3 months in high-risk patients (Class IIa, Level C).[1] For patients at high CV risk at baseline, an additional echocardiographic evaluation should be performed 2–4 weeks after the start of treatment,[31,61] particularly for those with HF and/or an arterial vascular disease, classified as high-risk individuals according to the ESC-ICOS risk assessment tables.[19,62]

At the end of the first year of echocardiographic surveillance, in the case of long-term treatment with VEGFi in asymptomatic subjects with no clinical events during the first year of therapy, a TTE every 6–12 months, instead of every 3–4 months, may be considered.[31]

Routine measurement of NPs may be considered in patients at moderate (Class IIb, Level C) and high and very high (Class IIa, Level C) risks of CV toxicity.[1,27]

There is currently insufficient evidence to prefer one antihypertensive drug over another in the treatment of hypertension in cancer patients. The majority of recommendations for the use of renin-angiotensin system inhibitors and dihydropyridine calcium channel blockers as first-line antihypertensive treatments comes from expert opinion.[61,63] Notwithstanding, the effectiveness of both these drugs classes in treating VEGFi-induced hypertension has been supported by several clinical trials, which also show the benefit of beginning antihypertensive therapy before VEGFi administration.[64,65]

Given their propensity to inhibit cytochrome P450, drugs like verapamil and diltiazem should be avoided as they have been shown to increase blood levels of VEGFi.[8]

Bruton's tyrosine kinase inhibitors

Bruton's tyrosine kinase (BTK) plays a key role in the signalling pathway required for the survival and proliferation of neoplastic B cells.[66,67] Currently, three BTK inhibitors (BTKi), ibrutinib, acalabrutinib, and zanubrutinib, have received Food and Drug Administration (FDA) approval for the treatment of B-cell malignancies, including early-stage and relapsed or refractory (R/R) marginal zone lymphoma (*Figure 1*; see Supplementary data online, *Table S1*).

Main cardiovascular toxicities

Ibrutinib forms an irreversible covalent bond with a cysteine residue in the BTK.[68] Ibrutinib administration, which is helpful in treating a variety of B-cell malignancies, has showed a certain degree of CV toxicity, also related to its lack of specificity for BTK.[69] Early studies revealed a substantial risk of bleeding, atrial fibrillation (AF), and hypertension, which makes the management of these patients particularly challenging.[70,71] Early ibrutinib studies revealed a 5%–8% incidence rate of AF;[72–74] however, more recent research based on extended follow-up time identified a higher incidence of new AF of 14%–16%.[70,75] In the research by Burger *et al.*,[72] 14% of patients had hypertension of any grade, with Grade 3 hypertension occurring in 4% of cases. Additional research has revealed a substantial increase in the risk of HF and supraventricular arrhythmias.[71]

The second-generation BTKi acalabrutinib has fewer CV adverse effects and less off-target activity.[76,77] An open-label, Phase II study involving 124 patients with mantle cell lymphoma has shown no new AF episodes.[78] In a recent Phase III randomized, open-label study, acalabrutinib showed non-inferiority progression-free survival compared with ibrutinib in patients with previously treated chronic lymphocytic leukaemia, with a decreased frequency of symptomatic CV events;[79] the incidence of AF of all grades was 9% in patients treated with acalabrutinib vs. 16% in patients treated with ibrutinib. Moreover, acalabrutinib patients had a reduced incidence of hypertension (9% vs. 23%) than patients who received ibrutinib.[79]

Zanabrutinib is a second-generation BTKi recently approved by the FDA as a second-line treatment of mantle cell lymphoma.[80] The study by Zhou *et al.*[81] analysed data from two Phase I/II studies[82,83] to verify the efficacy of zanubrutinib monotherapy in relapsed/refractory mantle cell lymphoma. Zanubrutinib was well tolerated, with treatment discontinuation and dose reduction for adverse events in 13% and 3% of patients, respectively. The most significant cardiotoxic events were hypertension, major haemorrhage, and AF with an incidence of 12%, 5%, and 2%, respectively.

Preliminary results on pirtobrutinib (LOXO-305), a highly selective, reversible, oral BTKi, showed not only the drug safety but also its effectiveness against a variety of B-cell malignancies.[84] Only 1% of patients had to discontinue treatment due to an adverse event related to the administration of pirtobrutinib. No patients developed Grade 3 AF; two patients developed Grade 2 AF, considered by investigators as unrelated to pirtobrutinib due to a history of previous AF. Haemorrhage and hypertension of all grades occurred in 5% of patients.

Recommendations

There is limited evidence to support CV monitoring in patients receiving these medications; strict BP control is encouraged[1,85] (Class I, Level B). Atrial fibrillation during treatment with ibrutinib has been shown to be predicted by initial ECG findings of left atrial enlargement.[86,87] Screening for AF is advised at each clinical visit during BTKi treatment[1,88] (Class I, Level C). Depending on the severity of AF, ibrutinib

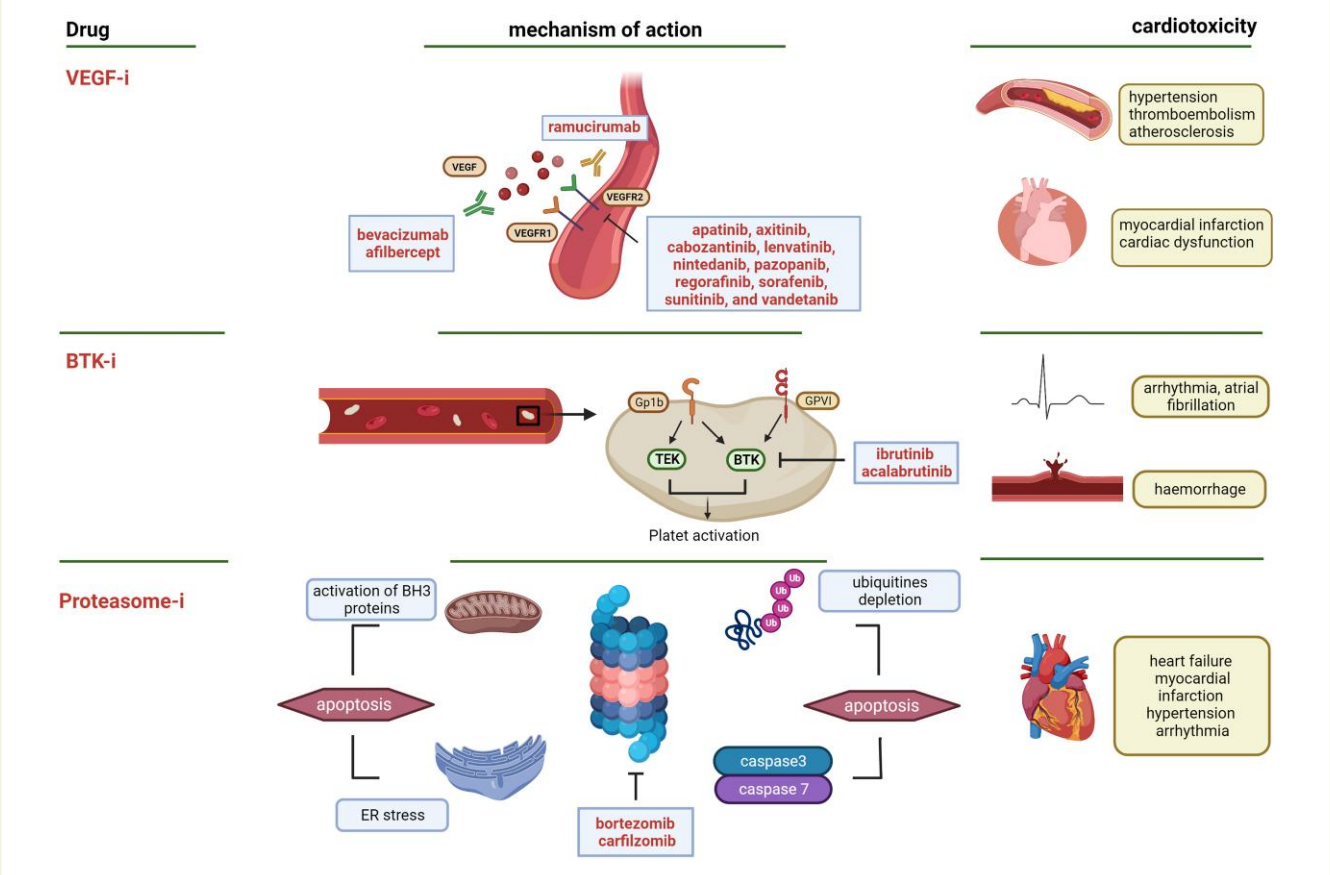

Figure 1 Mechanism of action and cardiotoxicity of drugs belonging to VEGF-i, BTK-i, and proteasome inhibitors. BTK-i, Bruton's tyrosine kinase inhibitor; ER, endoplasmic reticulum; VEGFi, vascular endothelial growth factor inhibitor; PI, protheosome inhibitor. Created with Biorender.com

treatment should be stopped and then resumed as soon as the cardiac condition returns to normal or is under control.[89] In most cases, ibrutinib is administered to an elderly population, characterized by high CV risk, undergoing therapy with anticoagulants and/or antiplatelets; given the risk of bleeding derived from co-administration of both of these drug classes, patients receiving concomitant ibrutinib and anticoagulants/antiplatelets should be carefully monitored for the risk of bleeding.[89,90]

Proteasome inhibitors

Bortezomib and carfilzomib are PIs that alter intracellular protein homeostasis resulting in the induction of apoptosis.[91] Bortezomib is a reversible and non-selective PI approved by the FDA in 2008 as an up-front treatment of newly diagnosed multiple myeloma[92] (*Figure 1*; see Supplementary data online, *Table S1*) . The demonstration of acquired resistance to bortezomib led to the development of carfilzomib, a second-generation PI, a potently selective irreversible PI. Carfilzomib proved effective in the treatment of refractory or pre-treated multiple myeloma patients, showing improved survival profiles and response rates to therapy.[93]

Main cardiovascular toxicities

Although both bortezomib and carfilzomib are associated with CV adverse events, carfilzomib was found to have a greater CV toxicity profile characterized by hypertension, arrhythmia, diastolic dysfunction, cardiomyopathy, and HF.[94,95]

In a prospective observational research, patients treated with carfilzomib showed a higher CV toxicity profile than the bortezomib-treated arm, with CV adverse events occurring in 51% vs. 17% of patients.[96] Furthermore, in carfilzomib-treated patients, CV adverse events occurred with a median time of 31 days, with more than 85% occurring in the first 3 months after the start of therapy. Similarly, a recent retrospective study found a 49% incidence of CV adverse events, with new-onset hypertension, HF, chest pain, myocardial ischaemic events, and arrhythmias.[97]

Recommendations

Cardiac biomarkers and TTE measured during therapy are critical diagnostic and prognostic tools that inform clinical decision-making during PI therapy.[96] Given the high incidence of CV toxicity, a TTE at baseline is recommended for all patients who are candidates for PI therapy together with a concomitant evaluation for cardiac amyloidosis (Class I, Level C).[1,31] Measurement of NPs has been shown to be effective in predicting the development of major adverse CV events (MACEs) in patients receiving PIs; several studies have reported a correlation between NP elevation and the risk of developing MACE in patients receiving carfilzomib or bortezomib therapy, while cTn value trends were not predictive for the development of CV events.[96,98] Measurement of NPs at baseline is therefore recommended for high- and very high-risk patients, and such measurement should also be considered in patients with lower risk levels (Class IIa, Level C).[1,27] Measuring NPs should

be considered throughout the first six cycles of therapy with carfilzomib or bortezomib during each cycle (Class IIa, Level B). Hypertensive and pro-thrombotic status should be strictly monitored; measurement of BP at each clinical visit is recommended (Class I, Level C), whereas measurement of BP at home for the first 3 months weekly and monthly thereafter has a lower level of evidence (Class IIa, Level C).[1]

Therefore, although there has not been a study to validate a specific time line and follow-up schedule for patients receiving PI, a 3–6 monthly ECG, blood tests (in particular NPs), measurement of BP and echocardiography monitoring during PI therapy are encouraged to rule out HF.[99]

V-Raf murine sarcoma viral oncogene homolog B (BRAF) and mitogen-activated protein kinase inhibitors

BRAF serine-threonine protein kinase inhibitors (BRAFi) are a class of target drugs that have been authorized for use in treating metastatic melanoma since 2005. As a result of the BRAF activating mutation, the mitogen activated protein (MAP) kinase pathway is chronically stimulated, resulting in a promotion of cell migration, angiogenesis, and suppression of apoptosis[100] (*Figure 2*; see Supplementary data online, *Table S1*). This mutation has been identified in around 60% of melanoma patients; more precisely, the V600E variant, which is present in roughly 90% of individuals with a BRAF mutation, is the most prevalent one.[101] Vemurafenib, dabrafenib, and encorafenib have been approved by the FDA for the treatment of metastatic melanoma; BRAFi monotherapy significantly improves survival in patients with advanced melanoma.[102] Nonetheless, BRAFi treatment led to hyperactivation of the mitogen-activated protein kinase (MEK) signalling pathway and drug resistance. This led to the development of MEK inhibitors (MEKi) (trametinib, cobimetinib, and binimetinib), which have proven particularly effective when administered in combination with BRAFi and are now the standard treatment regimen for BRAF-mutated melanoma patients.

Main cardiovascular toxicities

A recent meta-analysis found that BRAFi/MEKi combination therapy was associated with a higher relative risk of systolic dysfunction, hypertension, and pulmonary embolism than BRAFi monotherapy.[103] The likely mechanism is an altered nitric oxide bioavailability, inducing a pro-hypertensive state, together with disruption of the regulation of the renin-angiotensin system.[104]

A Phase III study compared the combination of dabrafenib and trametinib vs. dabrafenib and placebo. The combination therapy showed superior 3-year overall survival (44% vs. 32%) and improved 3-year progression-free survival (22% vs. 12%).[105] Combination therapy, however, showed a higher incidence of CV events such as hypertension (25% vs. 14%) and decreased LVEF (8% vs. 3%). In addition, both combination therapy and monotherapy with BRAFi were linked to development of myocardial infarction, AF, or QTc prolongation.[103]

Recommendations

Baseline risk stratification is mandatory before starting these therapies due to an increased rate of adverse CV events,[19] especially during combined treatments.[106] Baseline TTE is indicated for moderate- to high-risk patients, with monitoring at 6–12 months in high-risk cases (Class I, Level C), BP monitoring is indicated for HF prevention.[1] Electrocardiogram is advised baseline and 4 weeks following the start of treatment and every 3 months after that, particularly during cobimetinib/vemurafenib therapy. Currently, no data are available on the predictive efficacy of cTn measurement for the development of LVD in patients receiving BRAF and MEKi therapies. Therefore, there is currently no recommendation for its measurement during treatment. The measurement of cardiac biomarkers at baseline remains a useful tool for risk stratification of patients, since the finding of baseline high cTn and/or NP values represents an intermediate CV risk factor.[19]

Immune checkpoint inhibitors

Immune checkpoint inhibitors are monoclonal antibodies that target proteins involved in the mechanisms used by tumour cells to evade the immune response.[107] These proteins include programmed cell death protein 1 (PD-1) receptors on T lymphocytes (targeted by nivolumab and pembrolizumab), cytotoxic T lymphocyte antigen-4 (CTLA-4) (ipilimumab and tremelimumab), and PD-L1 (atezolizumab, avelumab, and durvalumab)[108] (*Figure 2*) . Since their first FDA approval in 2014, the number of cancer types with indication for treatment with ICIs has grown to over 50 including melanoma, lung cancer, and renal cell carcinoma[109] (see Supplementary data online, *Table S1*). Furthermore, ICIs have demonstrated better efficacy when used in combination (e.g. ipilimumab plus nivolumab).[110]

Main cardiovascular toxicities

Administration of ICIs has been correlated with a high frequency of drug-related adverse effects, ranging from 66% to 80%.[111–115] Myocarditis, pericarditis, pericardial effusion, cardiac tamponade, myocardial infarction, arrhythmias, and vasculitis are some of the main CV toxicities that have been observed, particularly in patients receiving combination therapy.[116,117]

The analysis of 30 different papers (a total of 4751 patients) characterized by the description of immuno-related cardiac adverse events found an incidence of such adverse events of 1.3%. Of note, more than 50% of these events were myocarditis (0.72%), followed by HF (0.15%), pericardial effusion (0.15%), and AF (0.06%).[118] Following treatment and the diagnosis of immune-related cardiac adverse events, 24.6% of patients died, the most common cause was myocarditis (80%).

The administration of ICIs has also recently been associated with the development and progression of atherosclerosis. Although the prevalence of this phenomenon is still difficult to determine, the evidence regarding the association between atherosclerosis and ICIs suggests the need for a more in-depth investigation of this phenomenon.[119,120]

Recommendations

Baseline ECG and troponin test should be performed,[121–123] while TTE should be required at baseline in a high-risk setting, and once treatment has begun, ECG, cTn, and NP should be checked regularly.[124–126] The performance of an echocardiographic examination prior to initiation of ICI therapy in patients at lower risk has a lower level of evidence (Class IIb, Level C).[1]

Among high-risk patients and those with high baseline cTn, TTE monitoring is encouraged.

Although fulminant myocarditis is a rare occurrence during ICI therapy, the high mortality rate (25%–50%) necessitates the development of suitable surveillance protocols for early detection of this condition. Clinical presentation of patients with myocarditis varies from asymptomatic elevation of cardiac biomarkers to severe cardiac dysfunction.[127] Patients with myocarditis may present with acute or chronic HF, including pericardial effusion with or without pericarditis.[128–130] Of relevance, myocarditis syndromes occur in the absence of obstructive CAD or other causes of HF. Common symptoms include dyspnoea, chest pain,

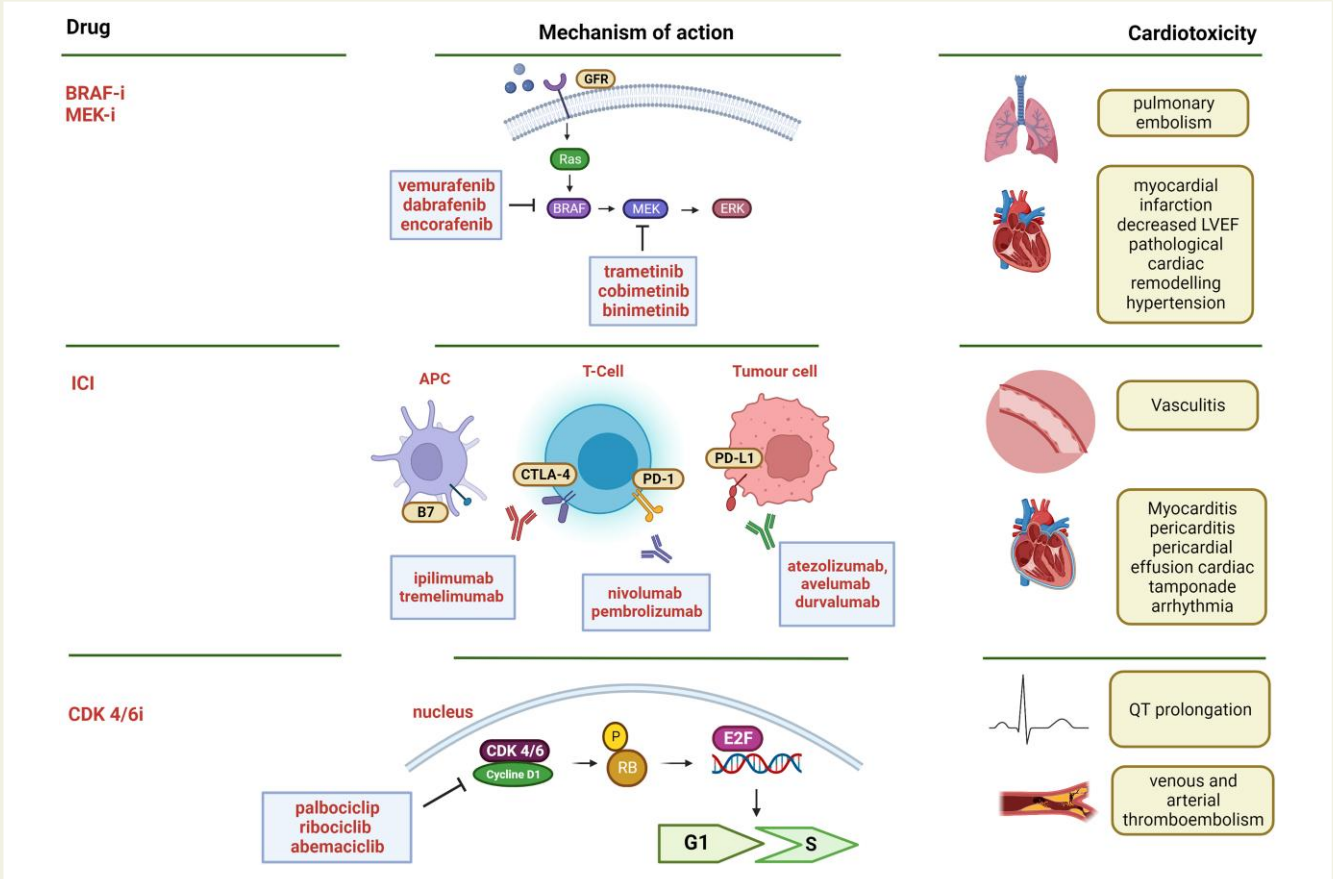

Figure 2 Mechanism of action and cardiotoxicity of drugs belonging to BRAF-i, MEK-i, ICI, and CDK4/6i. BRAFi, BRAF inhibitor; MEK-i, MEK inhibitor; ICI, immune checkpoint inhibitor; CDK4/6i, cycle-independent kinases 4/6 inhibitor. Created with Biorender.com

palpitations, and fatigue. Patients who develop myocarditis are also prone to develop MACE including cardiogenic shock, CV death, cardiac arrest, and severe rhythm disturbances up to complete heart block.[131]

Notably, myocarditis frequently co-occurs with myositis and myasthenia gravis, with initial possible dominance of muscle symptoms over cardiac symptoms.[131] The American Society of Clinical Oncology guidelines for the management of immune-related adverse events categorize myocarditis into four classes based on the severity of symptoms.[132] Electrocardiogram, echocardiogram, and based on consultation with a cardiologist, possible CMR or invasive tests like endomyocardial biopsy are all advised for all four classes.[132,133] Analysis of the time course of biomarkers, in particular cTn, which is useful for timing the performance of higher-level investigations,[125] is also advised.

In patients with ECG abnormalities, novel biomarker alterations, or developing symptoms, a prompt evaluation with TTE assessment is strongly advised, including the assessment of LVEF and CMR (modified Lake Louise criteria) when the suspicion of myocarditis is high.[134]

Although GLS measurement has shown a strong correlation with the development of major cardiac adverse event in patients who have developed myocarditis, there is not yet sufficiently strong evidence to integrate the study of GLS into the algorithm for diagnosing myocarditis.[126] Future studies are needed to confirm the validity of measuring this parameter in cancer patients.

Treatment of ICI-associated myocarditis involves first-line administration of high doses of prednisone or methylprednisolone (orally or intravenously depending on symptom severity), along with permanent discontinuation of immunotherapy if the myocarditis has a grade >1.[132] In case of failure to respond to corticosteroid administration, as assessed by clinical response and trends in cardiac biomarkers, administration of other immunomodulatory agents such as abatacept,[135] infliximab,[136] mycophenolate,[137] and plasapheresis[136] may be considered.

Cycle-independent kinase 4/6 inhibitors

Cycle-independent kinase (CDK) 4/6 play a key role in regulating cell mitosis. CDK 4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) have been approved for the treatment of hormone receptor (HR) positive (HR+)/HER2− metastatic breast cancer and as adjuvant treatment (abemaciclib) in patients with high-risk early stage breast cancer (*Figure 2*; see Supplementary data online, *Table S1*).

Main cardiovascular toxicities

CDK 4/6 and aromatase inhibitor combination therapy was associated with a risk ratio of 1.39 for CV toxicities compared with endocrine therapy alone.[138] Of the CDK4/6 inhibitor class, ribociclib has been linked to reversible, concentration-dependent prolongation of the QT interval, which seems to be specific to ribociclib.[139] Furthermore, the co-administration of ribociclib and letrozole[140] as well as tamoxifen[141] was associated with QTc prolongation.

A recent study using the FDA pharmacovigilance database evaluated the frequency of thromboembolic events related to the administration

of CDK 4/6 inhibitor. Thromboembolic events accounted for 3.5% of CV events occurring in conjunction with CDK6/4-i therapy. Futhermore, a higher-than-expected rate of arterial thromboembolic events for ribociclib has emerged.[142]

Recommendations

A baseline ECG to measure the QTc interval is recommended in all patients treated with ribociclib and then at 14 and 28 days (Class I, Level A).[139,141,143] As a mild CYP3A4 inhibitor, ribociclib should be used with caution when combined with CYP3A substrate drugs that have a limited therapeutic index, such as cyclosporine, tacrolimus, and everolimus. In addition, the concomitant administration of ribociclib and drugs that may prolong the QT interval (e.g. moxifloxacin, haloperidol, amiodarone) should be avoided. The ESC guidelines suggest a baseline ECG in patients treated with palbociclib and abemaciclib who are considered at high or very high risk of CTR-CVT.[1]

Last-generation androgen deprivation therapies

First-line therapy for advanced and metastatic prostate cancer involves lowering testosterone levels through androgen deprivation therapy (ADT). The first drugs used for medical castration in prostate cancer patients were gonadotropin-releasing hormone agonists.[144] This class of drugs acts at the level of the hypothalamus-pituitary-gonadal axis; pulsatile GnRH production by the hypothalamus is responsible for the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland, which in turn stimulates testosterone production in the testes. The administration of GnRH-A, by regulating its receptors in the pituitary gland, achieves a disruption of the hypothalamus-pituitary-gonadal axis within 3 weeks,[145] causing medical castration. GnRH-A administration initially causes a surge in testosterone levels and may cause a 'flare' reaction in patients with metastatic prostate cancer. Furthermore, it has been associated with increased CV risk and mortality especially in patients over 60 years of age.[146] Prostate cancer treatment options include the use of GnRH antagonists, and pre-clinical and clinical data indicate that this approach is linked with substantially lower overall mortality and CV events than agonist use.[147,148] As an GnRH antagonist, degarelix blocks GnRH receptors, resulting in a fast reduction in LH, FSH, and testosterone levels. It is believed that degarelix reduces FSH more than GnRH-A and is hence associated with a lower CV risk.[149] However, more study is required in this area, especially in view of the PRONOUNCE study findings.[150]

Despite the initial effectiveness of these therapies, acquired resistance frequently arises after a median of 7–11 months.[151,152] Castration-resistant disease and hormone-sensitive metastatic disease patients have both shown improved survival profiles when treated with abiraterone, an inhibitor of cytochrome CYP17 for testosterone synthesis, and enzalutamide, a drug that prevents testosterone from binding to its intracellular receptor[153,154] (*Figure 3*).

Main cardiovascular toxicities

According to a pooled analysis of three randomized controlled trials, those with pre-existing CVD who got a GnRH antagonist had a considerably lower risk of recurrent CV events than those who received a GnRH-A.[155] A more recent analysis from a Scottish registry in a large cohort of men ($n = 20\,216$) with newly diagnosed prostate cancer reported an increase in CV events with both luteal hormone releasing hormone- +antagonist (LHRH-A) [adjusted hazard ratio (HR) 1.3, 95% confidence interval (CI) 1.2–1.4] and degarelix (adjusted HR 1.5, 95% CI 1.2–1.9) compared with untreated patients.[149] Androgen deprivation therapy–induced testosterone decline is linked to an increased QTc interval. When comparing degarelix with leuprolide over a 12-month period in cancer patients ($n = 610$), secondary analysis found no difference in the percentage mean change in QTc between the pooled degarelix and leuprolide treatment groups.[156] In the PRONOUNCE study, which was terminated prematurely, there was no difference between degarelix and leuprolide in terms of MACE at 1 year.[151]

Abiraterone and enzalutamide administrations were linked to an increased risk of hypertension, as well as HF and myocardial ischaemic events, respectively[157,158] (see Supplementary data online, *Table S1*). Enzalutamide did not demonstrate an association with the risk of developing CV events, while abiraterone therapy has been associated with risk of developing CV events (relative risk 1.28, 95% CI 1.06–1.55).[159] Conversely, a prospective study of 8660 prostate cancer patients treated with the new hormonal agents found an increased risk of developing cardiotoxicity of all grades and high grade for abiraterone, and an increased risk of developing hypertension for both drugs.[160] Finally, Cone *et al.*[158] found that abiraterone was associated with an increased risk of developing overall cardiac events, myocardial infarction, arrhythmia, and HF, whereas enzalutamide administration was not associated with an increased risk of developing any CV events.

Recommendations

Electrocardiogram and QTc monitoring are suggested[161–163] during treatment for prostate cancer, as well as management of risk factors (metabolic profile, BP). In this regard, the 'ABCDE' paradigm (Aspirin and Awareness, Blood pressure, Cholesterol and Cigarettes, Diabetes and Diet, and Exercise) formulated and adapted by Bhatia *et al.*[164] could be a useful tool for controlling CV risk factors in patients treated with ADT.

Anaplastic lymphoma kinase inhibitors

Anaplastic lymphoma kinase inhibitors belong to the TKI family and are prescribed for the treatment of lung adenocarcinoma characterized by the anaplastic lymphoma kinase (ALK) driver mutation. Crizotinib, a first-generation drug active on both ALK and mitogen-activated extracellular signal-regulated kinase (MEK), has shown particularly effective against non–small-cell lung cancer (NSCLC) with ALK rearrangement[165] (*Figure 3*; see Supplementary data online, *Table S1*). The rapid development of resistance led to the development of second-generation drugs such as alectinib, brigatinib, and ensartinib.[166] The introduction of lorlatinib, a third-generation drug, was prompted by the emergence of resistance to even second-generation drugs and crizotinib's scarce effectiveness against brain metastases because of its poor blood–brain barrier penetration.[167]

Main cardiovascular toxicities

Cardiovascular toxicity primarily manifests as bradyarrhythmia, atrioventricular block, QTc prolongation, hypercholesterolaemia, hyperglycaemia, and peripheral oedema.[168] Rarely, HF development has been reported following crizotinib therapy.[167]

Recommendations

Baseline clinical assessment, including physical examination, BP measurement, ECG, lipid profile, and glycated haemoglobin measurement, is recommended (Class I, Level C). A baseline ECG is advisable; patients should have an ECG 4 weeks after treatment initiation and then every

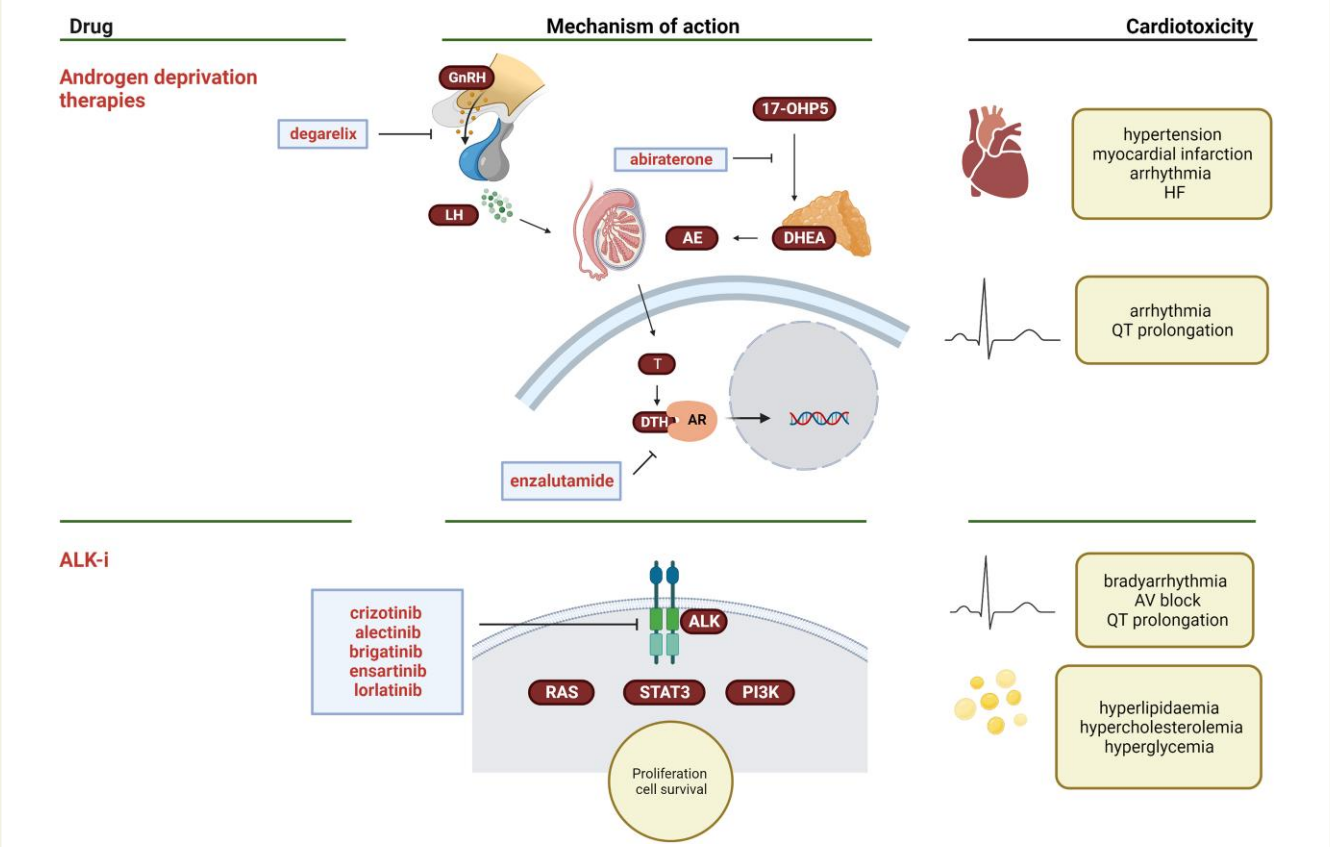

Figure 3 Mechanism of action and cardiotoxicity of drugs belonging to ADT and ALK-i. ADT, androgen deprivation therapy; ALK-i, anaplastic lymphoma kinase inhibitor. Created with Biorender.com

3–6 months, especially if the baseline ECG is abnormal. Home BP monitoring should be considered, as well as cholesterol levels measured at baseline and 3–6 months in patients receiving lorlatinib or crizotinib[1] (Class IIa, Level C).

Epidermal growth factor receptor inhibitors

Osimertinib is a third-generation oral epidermal growth factor receptor tyrosine kinase inhibitor used in the treatment of advanced NSCLC (*Figure 4*; see Supplementary data online, *Table S1*).

Main cardiovascular toxicities

Osimertinib administration has been associated in recent studies with the development of LVD, HF, conduction abnormalities, and arrhythmias.[169,170] A recent single-centre study that examined 123 cases of advanced NSCLC found that severe CV adverse effects occurred in 4.9% of cases and that 11% of patients experienced a significant reduction in LVEF <53%.[171] Based on data derived from the FDA Adverse Events Reporting System, the incidence of HF, AF, and QTc prolongation associated with the administration of osimertinib was higher than that of other TKIs.[170]

Recommendations

A comprehensive CV risk assessment (Class I, Level C) coupled with ECG evaluation is recommended (Class I, Level B).[1] Echocardiographic monitoring should be included, considering the risk of new LVD with osimertinib. Corrected QT evaluation and electrolyte checking (particularly magnesium) are indicated. When LVEF falls below 50% and by 10% from baseline values, withholding osimertinib may be considered. Affected patients with symptomatic or asymptomatic HF who do not experience improvement after 3 weeks of holding treatment may also be considered for discontinuation.[172]

Chimeric antigen receptor T cells

The CAR protein is a recombinant fusion protein composed of T-cell signalling and antigen recognition domains that can activate T lymphocytes against a particular antigen (*Figure 4*). In CAR-T treatment, T cells are stimulated to target the surface protein CD19, which is highly expressed in the majority of malignant B tumours.[173,174] Since mature cells in normal tissue do not express CD19 and do not release it in soluble form, CAR-T treatment is extremely selective.[175] In 2017 and 2018, the FDA approved axicabtagene ciloleucel and tisagenlecleucel, with the former finding use in the treatment of relapsed/refractory large B-cell lymphoma in adult patients and the latter for the use in the treatment of relapsed/refractory B-cell lymphoma in young adults up to 25 years of age and for acute lymphoblastic leukaemia in paediatric patients (see Supplementary data online, *Table S1*). The development of CAR-T cells that target different malignant B-cell surface antigens, such as CD20 or CD22, was subsequently driven by the large proportion of CD19-negative tumour cells in patients with disease recurrence.[176]

Main cardiovascular toxicities

Along with neurotoxicity, cytokine release syndrome (CRS), which is brought on by the fast immunological activation driven on by CAR T cells, is the most important side effect of treatment, occurring with a frequency of 90%.[177] The study conducted by Giavridis *et al.*[178] in a mouse model (SCID-beige mouse) showed that myeloid cells, including macrophages and monocytes, are the main cause of CRS development, releasing interleukin (IL)-1 and IL-6 together with other cytokines. IL-1 and IL-6 were also shown to be responsible for the activation of nitric oxide synthetase; the increased production of nitric oxide was therefore associated with the development of hypotension, which is a major life-threatening complication of CAR T-induced severe cytokine release. Other CV manifestations of CRS include tachycardia, dyspnoea, peripheral oedema, arrhythmias, cTn elevation, HF, and cardiogenic shock, with the most frequent cardiotoxic event being the development of profound hypotension necessitating therapy with vasoactive agents.[179] Although the pathophysiology of cardiac dysfunction during CRS is unknown, it is similar to cardiomyopathy associated with stress and sepsis, which is likely linked to IL-6, which has been shown to be a mediator of myocardial depression in inflammatory and infectious conditions.[180]

Between 24% and 36% of individuals who receive CAR-T therapy experience cardiotoxicity.[181,182] Patients who have had prior CVD, systolic, or diastolic dysfunction are at higher risk.[181] The incidence of MACE was found to be 21% in a study of 145 patients.[181]

Recommendations

Electrocardiogram and laboratory assessment are indicated in all patients. Transthoracic echocardiography at baseline coupled with a comprehensive metabolic panel (including Mg/Pho), cTn and NT-proBNP/BNP is recommended[1] (Class I, Level C), particularly in those with a history of CTR-CVT and CVD. An elevation in cTn is associated with a higher risk for further CV events: in case of this occurrence, re-evaluation should be warranted, including NPs, ECG, and echocardiography.[183] Treatment of cardiac adverse events should be risk-adjusted depending on product-specific and patient-specific characteristics based on the expected toxicities seen with various CAR T-cell therapies and disease states.

Neelapu *et al.*[184] proposed a treatment algorithm for CRS based on the classification proposed by Lee et al.[185]

In Grade 1 CRS, supportive therapy with adequate intravenous hydration is indicated along with discontinuation of any ongoing hypertensive therapies. In Type 2 CRS, in case of hypotension refractory to saline bolus administration, tocilizumab or siltuximab (IL-6 inhibitors) is recommended; if necessary, vasopressor administration is possible to maintain systolic BP >90 mmHg.

Given the close correlation between the development of CRS and CV events, early treatment with tocilizumab is vital in order to reduce CAR-T-induced cardiotoxicity. Alvi et al.[186] reported how in patients with increased cTn following CAR-T administration the risk of CV events increased for every 12-h delay to tocilizumab administration.

In patients with CRS Grade 3 or 4, co-administration of IL-6 inhibitors and corticosteroids is recommended.[184]

Human epidermal growth factor receptor 2–targeted therapies

Human epidermal growth factor receptor 2 is overexpressed or amplified in 15%–20% of metastatic breast cancers, advanced gastric cancer, and pancreatic cancer.[187] There are two classes of drugs that the FDA has presently approved for the treatment of HER2-positive tumours: monoclonal antibodies (trastuzumab, pertuzumab, trastuzumab emtansine, and trastuzumab deruxtecan) and TKIs (lapatinib, neratinib, and tucatinib) and antibody–drug conjugates (trastuzumab deruxtecan and trastuzumab emtansine).

Trastuzumab and pertuzumab coupled with chemotherapy are recommended as first-line treatments for HER2-positive metastatic breast, gastric, and pancreatic cancer (*Figure 4*; see Supplementary data online, *Table S1*).

Trastuzumab deruxtecan is an antibody–drug conjugate and a new-generation drug consisting of a humanized monoclonal anti-HER2 antibody coupled to a cytotoxic topoisomerase I inhibitor. Compared with trastuzumab emtansine, it has a better intracellular drug release profile and less systemic exposure to the cytotoxic topoisomerase I inhibitor.[188] Trastuzumab deruxtecan is now the recommended second-line treatment for metastatic HER2-positive breast cancer.[189]

Tucatinib, a third-generation TKI with high binding selectivity for HER2, was approved by the FDA in 2020 in combination with trastuzumab and capecitabine for the treatment of metastatic breast cancer.

Main cardiovascular toxicities

Trastuzumab cardiotoxicity is well known, occurring mainly as a decrease in LVEF (3.5%–17%) and HF (0.6%–4.1%),[190] particularly in patients with CV risk factors, advanced age, and previous anthracycline exposure.[191] Pertuzumab administration, characterized by the development of CV events similar to those of trastuzumab, has a rate of occurrence of HF and decrease in LVEF of 0.86% and 3.46%, respectively.[192] Compared with trastuzumab and pertuzumab, evidence from the literature on the cardiotoxicity of trastuzumab deruxtecan suggests a lower CV toxicity profile. Data from the phase II DESTINY-Breast01 study conducted in women with metastatic breast cancer previously treated with trastuzumab emtansine found a decline in LVEF in 1.6% of patients and the development of QTc prolongation in 4.9%.[193] Conversely, in the Phase II DESTINY-Gastric01 study conducted in patients with HER2+ gastric cancer, no relevant CV events were found.[194]

Despite the paucity of information on tucatinib cardiotoxicity, clinical trials have revealed reduced rates of cardiotoxicity when compared with other HER2 inhibitors, with CV events reported in <1% of patients.[195]

Recommendations

Monitoring of LV function with imaging and/or biomarkers is potentially useful. This is particularly critical when anthracyclines are used in the neoadjuvant setting, in a treatment regimen with sequential administration of trastuzumab. It is recommended to perform LV function surveillance based on LVEF and GLS before starting HER2-targeted treatments and at intervals of 3 months throughout their administration of HER2-targeted agents.[196,197] Recommendations for long-term cardiac imaging in patients with early invasive breast cancer vary according to patient risk. A follow-up TTE may be considered 6–12 months after the completion of treatment with anti–HER2-targeting agents in low-risk patients. In asymptomatic patients classified as medium/high risk, a TTE coupled with a clinical evaluation should be considered at 3–6 months and at 12 months after the end of therapy.[31] The actual value of using cardiac biomarkers as early indicators of the onset of cardiotoxicity related to anti–HER2-targeted therapies is presently not sufficiently supported by strong evidence. Future research is also required to clarify the function of biomarker monitoring in patient

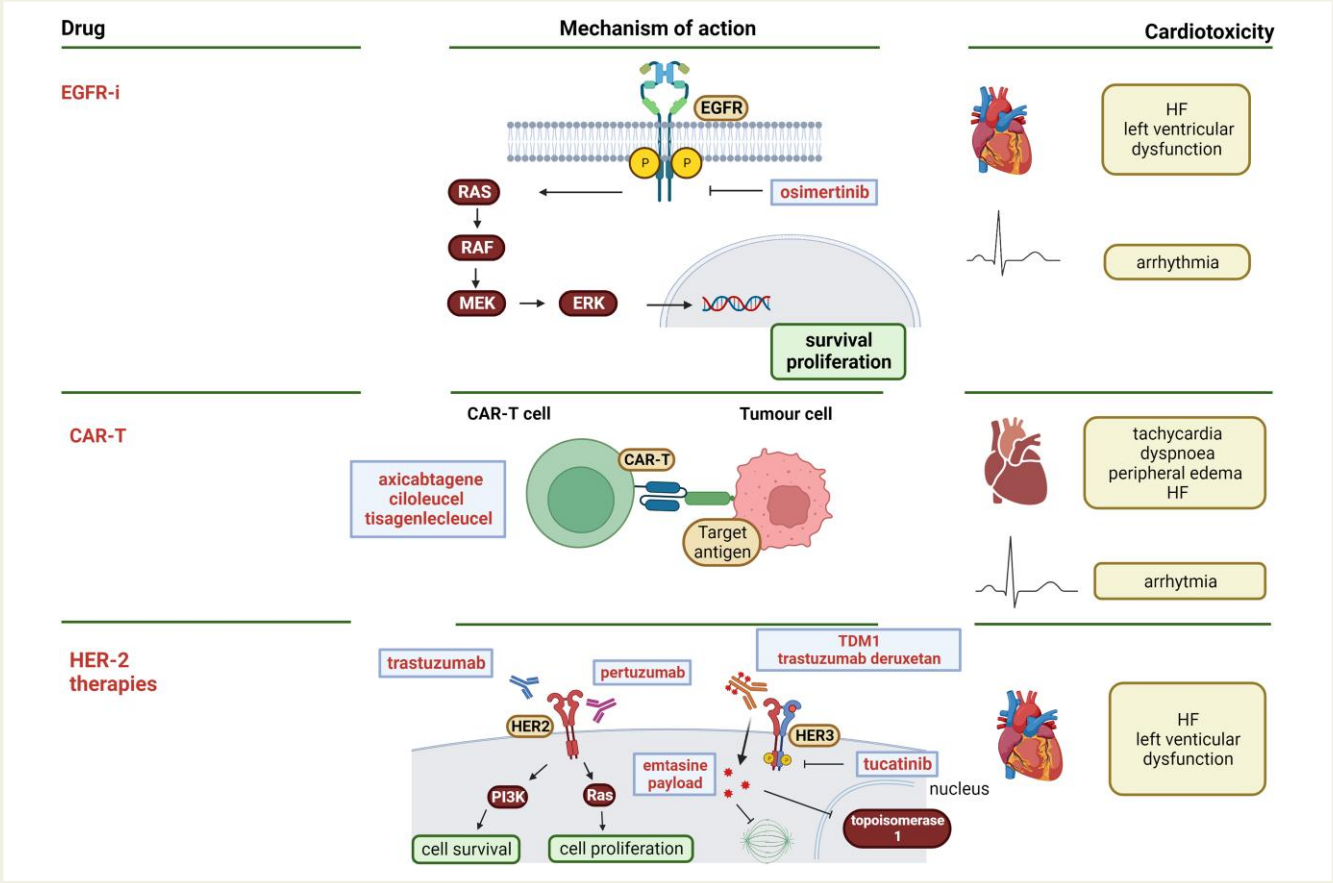

Figure 4 Mechanism of action and cardiotoxicity of drugs belonging to EGFR-i, CAR-T, and HER-2 therapies. CAR-T, chimeric antigen receptor T cell; EGFR-i, epidermal growth factor receptor inhibitor; HER-2, human epidermal growth factor receptor 2. Created with Biorender.com

follow-up during and after treatment with anti–HER2-targeted therapies. Baseline measurement of cTn and NPs is recommended in high- and very high-risk patients (Class I, Level C),[1,198] whereas in lower risk patients who have received or not received anthracyclines, the levels of evidence are lower (Class IIa, Level A and Class IIb, Level C, respectively).[1,28]

When to refer a patient to the cardio-oncology service

A holistic view in baseline evaluation and periodic management of candidates for chemotherapy is required, especially for high- or very high-risk subjects. In the circumstances listed below,[199] patients may benefit from receiving a cardio-oncology evaluation:

- High baseline CV risk profile prior to potential cardiotoxic therapy.
- Planned treatment with cancer therapies associated with substantial chance of experiencing CV toxicity.
- Patients with active CVD due to chemotherapy (hence stopped) who require active cardiological management.
- Patients previously receiving cancer therapies associated with a risk of late-onset cardiotoxicity.

The management of cancer patients undergoing cardiotoxic cancer therapy and the necessity for referral to a cardio-oncology service are based on the cardiologist's experience (number of cases actively managed) and expertise (time dedicated to specific cardio-oncology patients) in the field of cardio-oncology (as measured by the volume of patients seen per week and time spent on the clinical management of the patient; *Table 1*).

Long-term follow-up

Determining an adequate follow-up programme is crucial when patients have completed cardiotoxic cancer therapy successfully.[1] A re-evaluation of CV risk after potential cardiotoxic treatment is recommended due to the potential long-term cardiotoxic effects on the CV system, as well as patient-related CV risk factors, environmental factors, and stressors (e.g. acute viral infections, acute mental stressors, clinical depression).[200]

The ESC Guidelines recommend a CV evaluation 3–12 months after completion of cancer therapy according to the baseline risk profile.[1] Clinical scenarios include the following: (i) asymptomatic high-risk patients, who should undergo echocardiography and cardiac biomarker measurement at 3 and 12 months after completion of cancer therapy (Class I, Level B); (ii) asymptomatic moderate-risk patients, who should undergo echocardiography and biomarker measurement within 12 months (Class IIa, Level B); and (iii) asymptomatic low-risk patients, who should undergo echocardiography and biomarker measurement within 12 months (Class IIb, Level C). The goal is to identify patients at high risk, who require long-term surveillance. These patients should meet one or more of the following criteria: (i) a baseline risk level of

Table 1 Levels of competence of the cardiologist in the management of cancer patients undergoing cardiotoxic cancer therapy based on the volume of patients visited, knowledge, and need for referral to the cardio-oncology service

Level	Volume	Expertise	Referral to the cardio-oncology service
I (basic)	<1/week	• Critical cardiologic warnings • Side effects of cardiotoxic therapy	Targeted follow-up
II (intermediate)	2–5/week	• Essential pathophysiologic, oncologic, and pharmacologic expertise • Specific cardiologic warnings to treatments • Set-up of baseline management (history, risk stratification, diagnostic/therapeutic), with strong multi-disciplinary background • Set-up of targeted follow-up • Management of subclinical or minor clinical complications	Major events or high-risk patients
III (expert/referral centre)	>5/week	• Holistic and multi-disciplinary (stratification and cardiovascular complications imaging, biomarkers) cardio-oncological management extended to major complications (acute, severe) and higher risk profiles • Tumor boards	

high or very high risk determined by HFA-ICOS risk assessment tools; (ii) cancer treatments that have a significant risk of long-term CV complications; (iii) mild to severe CTR-CVT detected during cancer treatment; and (iv) new echocardiographic-detected heart function abnormalities, new elevations in cardiac biomarkers, or new cardiac disease symptoms.[1]

Current recommendations on CV therapy following completion of cancer therapy are largely based on expert consensus opinion. Due to the high frequency of recurrent HF, long-term CV therapy is often recommended for patients with moderate to severe symptomatic or severe asymptomatic CTRCD and should be taken into consideration in cancer survivors with mild or moderate CTRCD who fail to regain normal LV function. Weaning off CV treatment can be considered in a subset of patients with mild or severe CTRCD who have fully recovered and have normal TTE and cardiac circulating biomarkers. Following the discontinuation of CV medication in patients with a history of CV toxicities, additional evaluation of cardiac function using TTE and cardiac serum biomarkers is advised to ensure cardiac function is maintained. Targeted cardiac rehabilitation in cancer survivors with a high CV risk should be considered (Class IIa, Level B).[1]

Conclusions

Over the last two decades, the breakthroughs in pharmacological cancer treatments have improved the prognosis of patients with many types of cancer. Treatments targeting molecular signatures of specific cancers are associated with novel CV complications. Beyond the development of asymptomatic or symptomatic LVD, the spectrum of CV complications of modern cancer therapy may include acute coronary syndromes, thrombo-embolic events, hypertension, QTc prolongation and arrhythmias, myocarditis, pericarditis, and metabolic disorders. Recognition and management of CTR-CVT should be considered an essential component of cancer care. Continuous surveillance throughout the entire cancer patient's pathway is pivotal, with different intensity of monitoring, depending on the level of the patient's CV risk.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

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