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Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia

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Abstract

Remarkable progress has been made in the development of new therapies for cancer, dramatically changing the landscape of treatment approaches for several malignancies and continuing to increase patient survival. Accordingly, adverse effects of cancer therapies that interfere with the continuation of best-possible care, induce life-threatening risks or lead to long-term morbidity are gaining increasing importance. Cardiovascular toxic effects of cancer therapeutics and radiation therapy are the epitome of such concerns, and proper knowledge, interpretation and management are needed and have to be placed within the context of the overall care of individual patients with cancer. Furthermore, the cardiotoxicity spectrum has broadened to include myocarditis with immune checkpoint inhibitors and cardiac dysfunction in the setting of cytokine release syndrome with chimeric antigen receptor T cell therapy. An increase in the incidence of arrhythmias related to inflammation such as atrial fibrillation can also be expected, in addition to the broadening set of cancer therapeutics that can induce prolongation of the corrected QT interval. Therefore, cardiologists of today have to be familiar not only with the cardiotoxicity associated with traditional cancer therapies, such as anthracycline, trastuzumab or radiation therapy, but even more so with an ever-increasing repertoire of therapeutics. This Review provides this information, summarizing the latest developments at the juncture of cardiology, oncology and haematology.

Cancer-related diseases have been on the rise and cancer-related mortality has been on the decline, leading to a profound increase in the number of survivors of cancer over the past three decades¹. With this change has come greater recognition of the importance of the adverse effects of cancer therapies, some of the most important being cardiovascular in nature. Pre-existing cardiovascular disease can likewise complicate and even lead to the termination of cancer therapy (especially if it is not managed appropriately). Therefore, an important interaction exists between these two disease entities and their management. Considering the ageing of the general population, these dynamics are expected to increase in the years to come². Preparing individuals and society for this future is an important goal, and its pursuit has started in the form of the emerging field of cardio-oncology.

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Competing interests

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Ewer and Ewer provided a classic overview of the field of cardio-oncology in 2010, with an update in 2015 (REFS^{3,4}). Since then, the focus of cardio-oncology might not have shifted much, but the field of view has certainly become much broader, including not only cardiotoxicity but also many other cardiovascular diseases, especially vascular toxicity and arrhythmias (FIG. 1; Supplementary Fig. 1). This change is in large part related to the progress in cancer therapeutics from chemical compounds in the twentieth century to targeted agents around the turn of the millennium and to immunotherapies in the past decade (FIG. 2). This Review provides an updated overview of cardiotoxicity and arrhythmias associated with cancer therapies; vascular toxic effects are covered in a separate Review in this Issue⁵. As applicable, references will be made to available guidelines and consensus documents from various societies (Supplementary Tables 1–7) to reflect and discuss currently published consensus recommendations.

Cardiotoxicity of cancer therapies

Over the years, the term ‘cardiotoxicity’ has encompassed many specific disease entities and is very much in need of a universal definition. This need holds true for cancer therapy-related cardiomyopathies. The unifying element for these conditions is a decline in cardiac function, with differences in the defining criteria. Mechanistically, a decline in cardiac function can be due to direct (endogenous) cardiomyocyte damage (termed in this Review as ‘cancer therapy-related type I or primary (toxic) cardiomyopathy’), to alterations in perfusion, innervation or hormonal milieu (termed in this Review as ‘cancer therapy-related type II or secondary (indirect) cardiomyopathy’) or to inflammatory cell infiltration in the myocardium (termed ‘cancer therapy-related type III cardiomyopathy or myocarditis’) (BOX 1). Although cardiomyopathies associated with cancer therapies are rarely mediated by one single mechanism, this classification might serve the ultimate goals of fostering the proper selection of care and achieving the best possible outcomes.

Type I cardiomyopathy

Cancer therapy-related type I cardiomyopathies can occur with various cancer therapeutics. They are a consequence of direct toxic effects of cancer therapies on the myocardium and represent the prototypical toxic cardiomyopathy.

Conventional chemotherapies.—Conventional chemotherapeutics are chemical compounds intended to kill tumour cells by interfering with their high metabolic demand and mitotic activity. One of the most effective and prominent examples is anthracyclines, which intercalate between base pairs of DNA or RNA strands and thereby inhibit DNA or RNA synthesis⁶. Furthermore, anthracyclines inhibit topoisomerase II α , an important enzyme for DNA transcription and replication. Other effects include induction of iron-mediated oxidative stress that damages DNA, proteins and lipids, as well as histone modification that deregulates epigenomic and transcriptomic responses.

Cardiotoxicity is a dose-limiting adverse effect of anthracycline therapy (TABLE 1). Common terminology has been to label any evidence of cardiac injury occurring during and within 1 week of active cancer therapy as acute cardiotoxicity and thereafter as chronic cardiotoxicity, with either early or late onset (that is, within or after 1 year of completion

of cancer treatment)⁷. Acute anthracycline-related cardiotoxicity is a rare event, seen in less than 5% of patients. This cardiomyopathy presents with electrocardiogram (ECG) changes (in 20–30% of patients) and arrhythmias (up to 3% of patients), mainly sinus tachycardia but supraventricular tachycardia, heart block and ventricular arrhythmias can occur as well, leading to palpitations, presyncope and syncope, and even cardiac arrest. Acute declines in cardiac function can be seen as well, presenting with dyspnoea to the point of heart failure (HF)⁸. Finally, some patients develop pericarditis and have chest pain in addition to shortness of breath⁹. Pathologically, acute anthracycline-related cardiotoxicity resembles an acute toxic myocarditis with cardiomyocyte damage, inflammatory infiltrates and interstitial oedema¹⁰.

Chronic anthracycline-related cardiotoxicity is histopathologically characterized by vacuole formation, myofibril dropout, necrosis and fibrosis¹¹. Importantly, these changes predate the declines in ejection fraction and can be seen in myocardial biopsy samples, ranging from mild to severe, while nuclear or echocardiographic imaging still indicates normal cardiac function parameters¹². Moreover, even changes (increases) in myocardial injury early after anthracycline exposure do not necessarily correlate with changes (decreases) in left ventricular ejection fraction (LVEF) as assessed by either imaging modality¹². Nevertheless, a multigated acquisition scan-based study indicated that declines in cardiac function can be noted in certain individuals after a cumulative doxorubicin dose of 200 mg/m² and indicates the risk of progression through the HF stages¹³. The risk of HF progression gains particular meaning when one considers studies that present anthracycline-related cardiomyopathy as one of the worst types of cardiomyopathy¹⁴. However, data published in 2017 indicate a prognostic profile of anthracycline-related cardiomyopathy on a par with that of dilated cardiomyopathy, and an unrelenting decline in cardiac function does not have to be the norm with current regimens of cardiomyopathy and HF treatment¹⁵. The epidemiological scope of anthracycline-related cardiomyopathy is also in flux, with the reported incidence ranging from 0% to 57%, attributable to differences in study populations, definitions and tests used over time¹⁶.

The mechanisms of anthracycline-related cardiotoxicity have some overlap with its anticancer effects but also have unique and specific differences. For instance, anthracyclines inhibit topoisomerase II β and show a particular predilection for mitochondria in cardiomyocytes¹⁷. Mitochondrial injury is seemingly one of the cardinal elements of anthracycline-related cardiotoxicity, and damage to mitochondrial DNA has been proposed to be responsible for the long-term risk of cardiomyopathy associated with anthracycline exposure^{18–21}. Other studies have indicated that anthracyclines preferentially affect progenitor cells and thereby reduce the regenerative potential of the (injured) myocardium, the consequences of which then emerge over time, especially with any additional stressors^{22–24}.

Targeted cancer therapies.—The pharmacological action of classic chemotherapeutics is not very specific and, therefore, the potential to harm normal cells is fairly high. Consequently, therapies that specifically target the malignant molecular fingerprint were designed with the aim of yielding higher success rates with lower complication rates. A classic example is trastuzumab, a humanized antibody directed against HER2 (also

known as ERBB2), which is overexpressed in 15–20% of breast cancers²⁵ (BOX 2). Like other oncogenes, HER2 signalling increases cancer cell proliferation, tumour growth and metastatic spread; HER2 inhibition, therefore, translated into revolutionary clinical success^{26,27}.

Oncogenes

Oncogenes encode proteins that can transform cells into tumour cells. All but a few are derived from normal cellular genes (proto-oncogenes), and activation of a proto-oncogene into an oncogene generally involves a gain-of-function mutation.

However, much at odds with the promise of ‘smarter and safer designer drugs’, trastuzumab caused declines in cardiac function and even HF in nearly 30% of patients in early seminal clinical trials²⁸ (TABLE 2). Studies thereafter revealed an incidence of trastuzumab-related cardiotoxicity of 15–20% and of HF of <5%. Nonetheless, declines in cardiac function 10% can be seen in 40–45% of patients receiving trastuzumab in consecutive patient datasets^{29,30}. However, Ewer and Lippman pointed out unique differences between trastuzumab-related and anthracycline-related cardiotoxicity, leading to the terminology of cancer therapy-related type II (alternative) cardiotoxicity and cancer therapy-related type I (classic) cardiotoxicity, respectively³¹. A key differentiating element in these definitions is the recovery of cardiac function after cessation of trastuzumab therapy. However, the average LVEF of the original cohort of patients remained approximately 5% below baseline levels. Approximately 10% of patients had a LVEF that was more than 10% lower than the baseline level, and 20% of patients with a normal LVEF at baseline had a LVEF of less than 50% after treatment³². Other studies have indicated that as many as 75% of patients exposed to trastuzumab therapy might have an irreversible decline in cardiac function³³. Overall, 20% of patients experience an interruption of their trastuzumab therapy, and only half of these patients are able to resume the therapy, with a 15–40% likelihood of a recurrent drop in LVEF^{32,34,35}. These data outline the remarkable burden that trastuzumab-related cardiomyopathy can have in patients with breast cancer.

Elevations in the circulating levels of cardiac troponin (cTn) seem to identify those patients receiving trastuzumab who are at risk of an irreversible decline in cardiac function³⁶. Although plasma cTn level elevations have been noted in experimental studies with trastuzumab³⁷, these elevations are usually seen at the transition from anthracycline therapy to trastuzumab therapy. This observation highlights the previously described anthracycline–trastuzumab interaction, whereby trastuzumab impairs the repair response to anthracycline in cardiomyocytes⁴, which can then translate into cardiac injury and dysfunction. Inhibition of HER2 in the presence of other potent stressors to the myocardium, such as ischaemia and/or high afterload, can be similarly detrimental. Therefore, trastuzumab therapy can unmask any injury or stress on the myocardium that leads to the upregulation and activation of the HER2 stress response pathway. The interplay between various risk factors and the state of dependence of the myocardium on the HER2 signalling pathway might also provide an explanation for the seemingly contradictory findings between clinical trials and real-world registries. For instance, the risk of cardiotoxicity was low and confined to the active treatment period in the HERA trial³⁸, whereas an increasing risk of HF after trastuzumab

therapy has been seen in the SEER–Medicare database of patients³⁹. Of further note, in the SEER–Medicare database, the 3-year risk of HF was lower with anthracycline therapy than with trastuzumab therapy, but was highest when both were combined³⁹. Similar observations were made in the Cancer Research Network as well as other registry-based studies⁴⁰. In summary, the long-term cardiovascular implications of trastuzumab therapy remain to be defined.

Other HER2-directed therapies, such as lapatinib, pertuzumab and trastuzumab–emtansine, are associated with a lower risk of cardiotoxicity than trastuzumab. Furthermore, dual trastuzumab–pertuzumab HER2-directed therapy is not associated with a higher risk of cardiotoxicity than trastuzumab therapy alone^{41–43}. Of interest, the reported LVEF decline with the tyrosine kinase inhibitors (TKIs) afatinib and osimertinib, which target epidermal growth factor receptor (EGFR; also known as HER1), has been attributed to inhibition of HER2 in addition to EGFR inhibition⁴⁴.

TKIs are the second major group of targeted cancer therapies. These drugs interfere with the transfer of a phosphate group to a tyrosine residue of a protein, a critical regulatory cue in signalling pathways that control cell function, proliferation and survival⁴⁵. A prominent example of a TKI is imatinib, which neutralizes the BCR–ABL1 fusion protein, the molecular fingerprint of Philadelphia chromosome-positive haematological cancers, such as chronic myeloid leukaemia⁴⁶. Unexpectedly, cases of HF were reported in patients receiving imatinib, and in vivo and in vitro experiments indicated direct cardiotoxicity potential⁴⁷. Activation of the endoplasmic reticulum stress response, collapse of the mitochondrial membrane potential, release of cytochrome *c* into the cytosol and reduction in cellular ATP content were the originally implicated mechanisms leading to cardiomyocyte death⁴⁷. Over the years, experimental studies have both supported and challenged these initial observations^{19,48,49}. In clinical practice, cardiomyopathy and HF are very rarely seen with imatinib therapy (incidence of 1%)^{50,51}.

Philadelphia chromosome

Named after the city in which it was discovered in 1960 as the first tumour-specific chromosomal change in the form of a shortened chromosome 22 as a result of a reciprocal translocation that leads to the oncogenic *BCR–ABL1* gene fusion, which has a causal role in the malignant transformation of white blood cell precursors; the Philadelphia chromosome is found in 90% of patients with chronic myeloid leukaemia.

Endoplasmic reticulum stress response

Disruption of endoplasmic reticulum function leads to impairment of protein folding, accumulation of unfolded and misfolded proteins and risk of cell toxicity. The cell reacts to this endoplasmic reticulum stress by initiating the unfolded protein response to increase the capacity of the cell to handle and/or eliminate the accumulating unfolded or misfolded proteins or to initiate apoptosis.

As outlined in Supplementary Fig. 2, the incidence of cardiovascular toxicity differs considerably between different TKIs, and various mechanisms for the cardiotoxicity have been proposed over the years^{47,52–58}. Intuitively, the thought has been that cardiotoxicity is the consequence of drug promiscuity (that is, a function of the number of kinases inhibited)^{47,52,55,56}. However, experimental studies support the sentinel kinase theory and, as shown in Supplementary Fig. 2, the TKIs affecting the vascular endothelial growth factor (VEGF) and MAPK/ERK kinase (MEK) signalling pathways might be the TKIs associated with the highest risk of cardiotoxicity clinically^{52,59}. Furthermore, elegant studies have shown a remarkable spectrum of changes in the heart and cardiomyocytes even with TKIs targeting a single kinase⁶⁰. These changes encompass not only downregulation but also upregulation of kinase gene expression and activity. For instance, erlotinib might be associated with a low risk of cardiotoxicity not necessarily because of the sole inhibition of EGFR but rather because of the upregulation of signal transducer and activator of transcription 3 (STAT3) signalling, allowing adaptive fatty acid metabolism to maintain cardiac function⁶⁰. Likewise, studies in human inducible pluripotent stem cell-derived cardiomyocytes point towards insulin receptor signalling as a compensatory pathway in therapies inhibiting VEGF signalling⁶¹. Therefore, TKI-associated cardiotoxicity is complex and might be best assessed in an integrative (systems biology) manner^{62–64}.

Sentinel kinase theory

The theory that inhibition of one specific enzyme among all the enzymes that catalyse the transfer of a phosphate group from ATP onto a tyrosine, serine or threonine residue of a protein (kinome) is responsible for a specific action.

Management and prevention.—Consensus documents and guidelines on cardiotoxicity with cancer therapy (Supplementary Tables 1–3) generally agree that before starting any (potentially) cardiotoxic therapy, all patients should undergo a baseline assessment of cardiac function, with echocardiography as the preferred imaging modality (the American Society Echocardiography and European Association of Cardiovascular Imaging (ASE/EACI) recommend 3D echocardiography or 2D contrast echocardiography, plus global longitudinal strain (GLS), plus cTn measurement)⁶⁵, an assessment of any potential cardiovascular diseases and risk factors and optimal control of any of the cardiovascular abnormalities identified (ASE/EACI recommend cardiology referral in the case of any abnormal baseline parameter, for discussion of the pros and cons of cancer therapy and the initiation of cardioprotective strategies)⁶⁵. In this way, patients with cancer are approached in a manner similar to a preanaesthesia medical evaluation.

Recommendations for on-therapy and after-therapy evaluations have varied for anthracycline and non-anthracycline regimens. This difference is on the basis of the expected differences in cardiac function dynamics with these medications: a drop after therapy with anthracyclines versus a drop during therapy with non-anthracyclines. For therapies involving anthracyclines, the ASE/EACI consensus recommendation is to reassess all outlined parameters (LVEF, GLS and cTn) at completion and at 6 months after therapy, and if the cumulative doxorubicin-equivalent dose is $>240 \text{ mg/m}^2$, repeated measurements of LVEF,

GLS and cTn should be performed before each additional dose of 50 mg/m² (REF.⁶⁵). For cardiotoxicity related to non-anthracycline therapies, the ASE/EACI consensus is follow-up every 3 months with the outlined parameters while the patient is receiving cancer therapy, with two exceptions: patients receiving TKIs or VEGF inhibitors, who should have an additional early follow-up at 1 month, and patients with previous anthracycline exposure, who should have an additional evaluation at 6 months⁶⁵. For a surveillance strategy that is based on cTn levels, measurements are to be taken before and/or 24 h after each cycle of cancer therapy. Of note, the cumulative incidence of cTn level elevation increases with each cycle and can be seen with any form of high-dose chemotherapy. Patients who have a persistent elevation of cTn levels at 1 month of follow-up seem to be at the highest risk of cardiovascular events (mainly cardiomyopathy, HF and arrhythmias)⁶⁶. For GLS, a 15% relative change is considered to represent subclinical left ventricular dysfunction, but imaging should be repeated within 2–3 weeks⁶⁵. For LVEF, a drop of 10% from baseline to <53% is considered to represent cardiac dysfunction. Importantly, the load dependency of these measures needs to be taken into consideration⁶⁵.

The course of action for patients with abnormal GLS at either the relative threshold or the absolute threshold is not defined at present but clinical trials are ongoing to address this question in patients receiving anthracycline or non-anthracycline therapy, such as the SUCCOUR⁶⁷ and TACTIC⁶⁸ trials. In patients with reduced cardiac function and/or HF, treatment according to AHA/ACC HF stages is recommended^{69,70} (Supplementary Table 4). A critical question is whether to continue cancer therapy and by which parameters and cut-off values this should be decided. At present, there is no consensus that the LVEF should be 40% for cancer therapy in general⁷¹, whether the LVEF cut-off level can be as low as 30% even with anthracycline therapy⁷² or whether the LVEF should be >45% for patients receiving anthracyclines⁷³, and whether cancer therapy should be stopped if a LVEF decline of a certain degree to a certain level is recognized (for example, 10% decline to a LVEF of <50%)⁷² and other causes cannot be identified⁷⁴. Tests and prediction models of risk, reversibility and prognosis of cardiotoxicity would be extremely helpful. An illustrating example is the utility of cTn levels in defining which patients are at risk of irreversible LVEF decline with trastuzumab therapy, as outlined earlier.

The modes of prevention of cancer therapy-related cardiotoxicity have varied drastically. For anthracyclines, the considerations have been the use of epirubicin instead of doxorubicin, although studies have suggested that when adjusted for equivalent dose, no significant difference is seen between these two drugs; prolonged infusion rates to reduce peak circulating concentrations of the drug; use of liposomal formulations to reduce myocardial accumulation; concomitant use of dexrazoxane, which was introduced as an iron chelator but also has cardioprotective effects through interaction with topoisomerase II β ¹⁷; and use of an alternative, non-anthracycline-based therapy, which might or might not have equivalent anticancer efficacy. Various cardiovascular disease medications, especially the second-generation and third-generation β -blockers carvedilol and nebivolol, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, spironolactone and statins, have been shown to have a preventive effect against anthracycline-related cardiomyopathy, although not unequivocally^{7,75}. Additional novel approaches to test in future studies include the use of erythropoietin, which might act through the progenitor cell pool^{76–78}. Another

potential approach is the use of patient-specific, inducible pluripotent stem cell-derived cardiomyocytes to identify patients at high risk of cardiotoxicity with anthracyclines^{79,80}. However, the long turnaround time for this test currently does not allow the expeditious decision-making that is often needed for cancer therapy. Finally, although some gene variants predisposing to cancer therapy-related cardiotoxicity have been defined and their use for patient screening and for selecting therapy is conceptually attractive, testing for these variants has not yet been adopted in clinical practice⁶³.

Effective cardioprotective therapies have not been defined for trastuzumab-induced cardiomyopathy, because the two trials conducted so far (one on bisoprolol and perindopril and one on candesartan) did not meet their primary end points^{81,82}. Although initial reports suggested that cessation of trastuzumab therapy suffices for the recovery of cardiac function, other studies indicated that institution of guideline-directed cardiovascular therapy helps to decrease the burden of irreversible cardiac decline^{30,83}. Re-exposure to trastuzumab after recovery of cardiac function has been deemed possible, although a redecline might occur and LVEF needs to be followed up serially. Severe increases in blood pressure (systolic blood pressure >180 mmHg) should be avoided because experimental studies and clinical reports show that the risk of decompensating HF is increased when (very) high afterload conditions are combined with HER2 inhibition^{84,85}. This recommendation is also important for patients receiving VEGF-inhibitor therapies (see the next section). These considerations are important for the concept of the (functional) cardiovascular reserve capacity, which is a very simple but important and practical framework for the general approach to patients with cancer at risk of cardiomyopathy and HF. Related conceptual models that predict risk on the basis of this concept remain to be validated. The role of improving the cardiovascular reserve before, during and after cancer therapy has been addressed in previous reviews and a 2019 AHA statement^{86,87}.

Type II cardiomyopathy

In contrast to cancer therapy-related type I cardiomyopathies, in cancer therapy-related type II cardiomyopathies, factors other than a direct toxic effect on cardiomyocytes are the main reason for or contribute substantially to a decline in cardiac function. Recognizing these factors is important for patient management and outcomes.

Conventional chemotherapies.—Therapy with 5-fluorouracil (5-FU) and capecitabine has been associated with cardiotoxicity in up to 20–30% of patients (depending on the patient population studied and criteria used)⁸⁸ (TABLE 1). Induction of profound and diffuse vasoconstriction that involves the coronary microcirculation is one possible mechanism of cardiotoxicity, especially in patients who show a rather quick recovery and have a type of cardiomyopathy referred to as Takotsubo syndrome^{89–96}. In other patients, permanent damage can evolve as a consequence of vasospasm-related myocardial infarction (MI) or direct toxic injury to the myocardium and the vasculature⁹⁷. Indeed, direct injury to cardiomyocytes, even similar to anthracycline-related damage, has been reported with 5-FU^{98–102}. This direct cardio toxic effect has been attributed to several mechanisms, among them induction of oxidative stress and metabolic derangements in cardiomyocytes^{103,104}. 5-FU is catabolized to fluoroacetate, which interferes with Krebs cycle activity, leading

to depletion of high-energy phosphates that are critical for normal cardiac function^{105,106}. Importantly, the metabolism of 5-FU is controlled by dihydropyrimidine dehydrogenase (DPD), and deficiencies in this enzyme have been associated with an increased risk of 5-FU-related toxic effects, although the link with cardiotoxicity remains debated^{107,108}. Arguing against a link with DPD deficiency is the occurrence of 5-FU-related cardiotoxicity in patients with normal DPD activity¹⁰⁴. Nonetheless, treatment with the 5-FU prodrug tegafur (5-fluoropyrimidine) in combination with the DPD inhibitor uracil, which allows the delivery of 5-fluoropyrimidine while blocking the generation of toxic metabolites, has been shown to reduce 5-FU-related cardiotoxicity^{104,108}.

Targeted therapies.—HF presentations and declines of cardiac function, even presentations of Takotsubo cardiomyopathy, have been reported with VEGF inhibitors, such as bevacizumab. Given that bevacizumab does not have the confounding aspects of multitarget effects of TKIs and has not been shown to be directly toxic to cardiomyocytes, one might conclude that inhibition of the VEGF signalling pathway alone suffices to induce ‘cardiotoxicity’ and via effects different from conventional chemotherapy-induced cell toxicity^{109–111}. As reviewed in detail previously¹¹¹, inhibition of the VEGF pathway impairs vascular reactivity and the angiogenic response to ischaemia and increased afterload conditions in the heart. This effect might explain the relevance of coronary artery disease (CAD) and hypertension as risk factors for VEGF inhibitor-related cardiomyopathy. However, any pre-existing or evolving, absolute or relative, structural or functional coronary (micro) vascular deficit can result in a risk of cardiomyopathy with VEGF-inhibitor therapy¹¹¹. Of note, whereas capillary regression is seen in endocrine organs rapidly after initiation of VEGF-inhibitor therapy, this regression is not observed in the heart^{112–115}. Therefore, a decline in cardiac function with VEGF-inhibitor therapy might not be seen unless additional stressors increase the activity of (and/or the demand for a compensatory response via) the VEGF pathway.

Additional pathways of interest include the insulin receptor pathway, which can serve a compensatory role when VEGF signalling is inhibited⁶¹, and the platelet-derived growth factor subunit- β pathway, which has a critical role in pericyte viability and is a critical off-target pathway contributing to sunitinib-related cardiotoxicity. Sunitinib, which inhibits multiple receptor tyrosine kinases, including VEGF receptors and platelet-derived growth factor receptors, destabilizes the coronary microvascular endothelial network and reduces the coronary flow reserve and cardiac contractile reserve.

Immunotherapies.—Immunomodulatory strategies have been developed with the aim to train the host immune cells to target and destroy cancer cells. One type of cancer immunotherapy, known as chimeric antigen receptor (CAR) T cell therapy, is based on the recognition by engineered T cells of signature surface antigens on cancer cells^{116,117} (BOX 3). The first CAR T cell strategy that was developed targeted melanoma-associated antigen 3 (MAGEA3)¹¹⁸. Despite no signal for toxicity in preclinical testing, two patients who received this therapy died of HF within a few days¹¹⁹ (TABLE 3). Severe acute myocarditis with T cell-mediated cardiac injury was the underlying histopathology. Intriguingly, this

effect was not related to cardiac expression of MAGEA3 but instead was caused by cross-reactive recognition of titin, a striated muscle-specific protein¹²⁰.

The first CAR T cell therapy directed against HER2 was also associated with toxicity, inducing the development of acute respiratory failure, shock and cardiac arrest within 12 h (REF.¹²¹). Diffuse alveolar damage was seen on autopsy and was thought to be the initial insult that was then followed by multiorgan ischaemia and systemic haemorrhagic microangiopathy. On-target and off-tumour reactivity against HER2 in normal pulmonary tissue on first-pass clearance in the lungs with subsequent pneumonitis and cytokine storm was postulated as the underlying mechanism of anti-HER2 CAR T cell toxicity. However, the associated adverse effects might also have been a consequence of the dose because this patient received the highest permitted number of cells. In agreement with this idea, subsequent studies with a different HER2-specific CAR T cell therapy at much lower doses (and without conditioning chemotherapy) have proven it to be safe¹²².

The currently best-studied type of CAR T cell therapy is directed against CD19 and is approved by the FDA as tisagenlecleucel (Kymriah) for children and young adults with relapsed or resistant B cell acute lymphoblastic leukaemia and adults with relapsed or refractory diffuse large B cell lymphoma¹¹⁶. The adverse effect profile associated with anti-CD19 CAR T cell therapy is extensive, but the best-known adverse effect of this therapy, and of any CAR T cell therapy, is cytokine release syndrome (CRS)^{116,123–125}.

Cytokine release syndrome

(CRS). A systemic inflammatory response that can be triggered by a variety of factors such as infections, antibody-based immunotherapies and chimeric antigen receptor T cell therapy. CRS is caused by the rapid release of a large amount of cytokines into the circulation, leading to fever, nausea, headache, rash, tachycardia, hypotension and respiratory distress.

The cardiovascular sequelae with CRS in the setting of CAR T cell therapy include tachycardia (with mild CRS) and hypotension, arrhythmias and decreased cardiac ejection fraction (with severe CRS)¹²⁵. Cardiac arrest is rare, but can occur even 1 week after therapy initiation, as reported in one patient in conjunction with a precipitous drop in LVEF^{116,123–125}. The cardiac function dynamics in CRS are thought to be similar to those seen in patients with systemic inflammatory response syndrome or sepsis but can differ, with differences in the cytokine profile and a general lack of endotoxin exposure¹²⁶. Tumour necrosis factor (TNF) and IL-1 β are considered the two leading cytokines accounting for the drop in LVEF in sepsis, via nitric oxide-dependent and nitric oxide-independent alteration of myocardial contractility¹²⁷. Counterintuitively, a reduction in LVEF is not a sign of poor prognosis in patients with sepsis, and the presence of new-onset left ventricular dysfunction does not increase the risk of long-term HF outcomes in severe sepsis and septic shock¹²⁸. Indeed, patients who survived septic shock showed a dynamic LVEF profile with decline during the acute phase and recovery after 7–10 days, whereas LVEF remained static in patients who subsequently died¹²⁹. This observation seems to be the consequence of cardiac remodelling, that is, an increase in ventricular compliance that leads to ventricular dilatation,

which subsequently accounts for a lower calculated LVEF while stroke volume remains the same and cardiac output is not depressed. These dynamics reduce the likelihood of a myocardial hypercontractile response in the hyperdynamic circulatory state characteristic of septic shock, which translates into poorer outcomes in these patients. In agreement with this concept, β -blocker therapy in patients with septic shock leads to improved outcomes¹³⁰. Importantly, although protected from hyperdynamic circulatory exhaust, the hearts of patients who survive sepsis remain responsive to catecholamine stimulation during septic shock and show increased contractility and cardiac performance with dobutamine therapy¹³¹. These details of cardiac function dynamics and their relationship with outcomes have not been fully described in patients with CRS.

A second type of T cell-directed immunotherapy, known as bispecific T cell engager therapy (BiTE therapy), can lead to a similar spectrum of complications as CAR T cell therapy, but not as commonly or severely^{132,133}.

Bispecific T cell engager therapy

(BiTE therapy). BiTE antibody constructs are designed to create an immunologic synapse between an effector T cell and a tumour cell by simultaneously binding to the T cell activation molecule CD3 and a tumour-associated antigen, which is CD19 on B cells in the case of blinatumomab (approved for the treatment of B cell acute lymphoblastic leukaemia).

A third and the leading type of cancer immunotherapy at present is immune checkpoint inhibition (BOX 4). Immune checkpoint inhibitors (ICIs) are a unique type of antibody-based targeted therapies. This approach leverages the principles of immunosurveillance, its under-pinning by cancer cells and its reactivation by targeting the 'breaks' or 'checkpoints' of effector T cells^{134–136}. Although the main cardiotoxicity associated with ICIs is myocarditis, Takotsubo syndrome and global cardiomyopathies have also been reported in patients receiving ICIs^{137,138}. The mechanisms of these types of ICI-related cardiotoxicity are not entirely clear. As in all patients with myocarditis, various stressors could have a contributing role¹³⁹. As in other patients with Takotsubo syndrome or global cardiomyopathy, the main clinical presentations are acute coronary syndrome and acutely decompensated HF¹³⁹.

Radiation therapy.—Radiation therapy has always been an integral part of cancer treatment. The effectiveness of radiation therapy against cancer cells is mediated primarily by induction of DNA damage that then leads to cell senescence and cell death¹⁴⁰. Generation of oxidative and nitrosative stress with modification of various cell molecules and structures has an additive effect on these outcomes.

Cell senescence

A process defined as irreversible cell cycle arrest, driven by a variety of mechanisms, including telomere shortening, other forms of genotoxic stress, mitogens or inflammatory

cytokines, that culminate in the activation of the tumour suppressor p53 and/or the cyclin-dependent kinase inhibitor p16.

The cardiomyopathy seen with radiation therapy is of the restrictive subtype (TABLE 1). This cardiomyopathy typically presents as HF with preserved ejection fraction¹⁴¹. Importantly, cardiomyocytes are fairly resistant to radiation injury¹⁴². However, cardiomyocytes are not immune to damage to their DNA and organelles; oxidative stress and metabolic abnormalities can also evolve with radiation therapy¹⁴³. Experimental studies have demonstrated degeneration of cardiomyocytes in irradiated hearts^{144,145}, but this cardiomyocyte damage seemingly follows changes in the coronary microcirculation¹⁴⁶. The first response in radiation-related cardiotoxicity is activation of the coronary microvascular endothelium (to a large part related to the activation of the nuclear factor- κ B (NF- κ B) signalling pathway), with an increase in the expression of chemoattractant and adhesion molecules, which favours leukocyte infiltration. In addition, an increase in vascular permeability leads to the extravasation of blood content such as fibrin and its deposition in the interstitium as amyloid-like structures¹⁴⁷. Increased endothelial dysfunction together with a reduction in thrombomodulin levels contributes to thrombus formation. Depending on the extent of radiation-induced injury, enfacement and swelling of endothelial cells can also be seen, further contributing to microvascular obstruction. Capillary density might not change or might even slightly increase during the acute phase. However, over time, the proliferative (angiogenic) response of coronary microvascular endothelial cells is exhausted, and the area of the functionally competent microvasculature is reduced. This loss of microvasculature can result in ischaemia and cardiomyocyte loss with replacement fibrosis. Myocardial fibrosis is further provoked by the inflammatory response and premature senescent changes in tissue fibroblasts. These changes along with activation of the transforming growth factor- β (TGF β)–SMAD signalling pathway in these fibroblasts induce the production of excessive amounts of collagen. A similar type of inflammatory and fibrotic injury response to radiation therapy can be observed on the valves and the pericardium^{148,149}. Pericardial and valvular disease have long been known to contribute to HF, the final common pathway of radiation-induced heart disease. Defining the relative contributions of ischaemia, restriction, constriction, volume overload and pressure overload is important for the treatment of patients with radiation-induced heart disease but might not always be possible. Some of these factors can be differentiated by dose exposure, because several studies have revealed that the risk of pericarditis (and therefore its long-term complications) is low with dose exposures below 35–40 Gy (REF.¹⁵⁰).

Management and prevention.—The identification and management of factors that contribute to or drive cancer therapy-related type II cardiomyopathies are essential for the management of these conditions. These factors differ by the type of cancer therapy, as outlined in the following paragraphs. As a common principle, cancer therapies contributing to the cardiotoxicity should be discontinued at least until cardiac function recovers and the precipitating or contributing factors are controlled. Resumption of these therapies is subject to risk–benefit assessment and discussion (with close follow-up of patients).

A main element in the management of 5-FU-induced or capecitabine-induced cardiotoxicity is potent vasodilatory therapy. Nitrates might suffice on the epicardial level but can be insufficient on the coronary microcirculatory level¹⁵¹. Calcium-channel blockers (for example, diltiazem or long-acting nifedipine) are more efficacious in this regard. A history of cardiac disease (in particular ischaemic heart disease) significantly increases the risk of 5-FU-induced cardiotoxicity¹⁵². Some data suggest that renal insufficiency rather than age (>55 years) is also a risk factor for 5-FU-induced cardiotoxicity^{104,151}. The mode of administration of the cancer therapeutic is an important factor: the risk of cardiotoxicity is higher with continuous administration (over 2 days) than with bolus infusion (over 3 h); the latter is, therefore, a preventive strategy¹⁵³. In addition, patients at risk of cardiomyopathy, especially those with previous events, should be given vasodilatory therapy. However, this approach might not provide full protection, and continuous ECG monitoring is advised. In some patients in whom left ventricular function decline is highly suspected in the absence of traditional clinical signs and symptoms, on-therapy follow-up with measurement of plasma B-type natriuretic peptide (BNP) levels and/or by echocardiography might prove useful. Other approaches include the use of alternative preparations of 5-FU, such as tegafur–uracil and tegafur–gimeracil–oteracil (known as S-1)¹⁰⁴. Uridine triacetate (Vistogard) was approved in 2015 for the treatment of life-threatening 5-FU-related and capecitabine-related toxicity¹⁵⁴. This compound delivers high concentrations of uridine, which competes with 5-FU metabolites¹⁵⁴.

For VEGF-inhibitor therapy, the evaluation and treatment of any possible contributing factor is the best approach, as discussed earlier and in greater detail elsewhere^{111,155} (Supplementary Fig. 3). Proper management of hypertension is a general principle for the prevention of HF, but especially in patients receiving VEGF-inhibitor therapy, and an argument can be made for aiming towards the SPRINT¹⁵⁶ blood pressure target of <130/80 mmHg in these patients. Other conditions of increased cardiac afterload, such as aortic stenosis, might not be as easily amenable to therapy, especially if they do not yet meet the criteria for intervention but are still severe enough to trigger a hypertrophic response in the myocardium and a reduced cardiovascular flow reserve. The same reduction in the cardiovascular flow reserve might be present in patients with diabetes before any cancer therapy, and correction might also not be possible in these patients, especially not in a short time. Although a clinical history of CAD suffices as a risk factor for VEGF inhibitor-related cardiomyopathy, whether a history of MI suffices as the sole critical element leading to VEGF inhibitor-related cardiomyopathy or whether, for instance, the extent of baseline and inducible ischaemia should be defined is unknown^{157–159}.

Cardiovascular flow reserve

The capacity of the coronary vascular bed to increase blood flow maximally to the myocardium, often expressed as a ratio with regard to baseline blood flow.

The treatment of choice for CRS grade 3 or greater in patients receiving CAR T cell therapy is an IL-6 antagonist (such as tocilizumab or siltuximab)¹²⁵. The prophylactic use of these agents might prevent the development of CRS and is currently under investigation. A concern is that this strategy could negate the main anticancer effect of the CAR T

cell therapy. The same concerns apply to prednisone, an anti-inflammatory glucocorticoid therapy that is recommended for severe CRS. In patients with evidence of circulatory compromise (shock), haemodynamic support with vasopressors is also recommended¹⁶⁰.

For patients receiving radiation therapy, reduction of dose exposure is the best intervention. Some experimental studies have indicated a benefit of statin and angiotensin-converting enzyme-inhibitor therapy, and anti-inflammatory and antioxidant therapies are theoretically attractive, but none of these approaches has been proven in clinical practice. These strategies should be tested, but challenges include defining the optimal treatment window and covering the diverse spectrum of cardiac disease associated with radiation therapy. These concerns apply to any strategies newly identified in preclinical studies, including TGF β receptor type 1 inhibitors, sestrin 2 inducers, recombinant neuregulin 1 and miR-21 inhibitors¹⁶¹. The ASE/EAVI and the Society for Cardiovascular Angiography and Interventions provide consensus algorithms for follow-up after radiation therapy^{162,163} (Supplementary Fig. 4).

Type III cardiomyopathy

Conventional chemotherapies.—The classic example of conventional chemotherapy that can induce myocarditis is cyclophosphamide¹⁶⁴. Particularly at high doses, cyclophosphamide can cause haemorrhagic myocarditis¹⁶⁵. The threshold dose for cyclophosphamide-induced myocarditis is not defined. A dosage of >270 mg/kg for 1–4 days or doses of 1.55 g/m² are considered to be associated with a substantial risk of cardiotoxicity¹⁶⁶. However, doses as low as 100 mg/kg can generate cardiotoxicity¹⁶⁶. At an in-between dose of >150 mg/kg, the incidence of acute HF is 7–33%¹⁶⁶. Interindividual variation in metabolism might be a factor contributing to the differences in incidence. Metabolites of cyclophosphamide can induce endothelial capillary injury with oedema, haemorrhage and thrombosis¹⁶⁶. Tachyarrhythmias can be induced as a result of myocardial injury, and more advanced stages present as HF. Cyclophosphamide therapy can also induce pericardial effusion, even with acutely life-threatening tamponade. Progressive myocardial mechanical failure can also evolve. Mortality in patients with cyclophosphamide-induced myocarditis is 2–17%¹⁶⁶.

Targeted cancer therapies.—Immune mechanisms have been suggested to contribute to the anticancer effects of trastuzumab¹⁶⁷, but whether and to what degree immune mechanisms contribute to trastuzumab-induced cardiomyopathy is not known; at present, only little experimental evidence is available¹⁶⁸. Only one case has been reported of fulminant acute myocarditis with the TKI sorafenib, which led to cardiogenic shock with a fatal outcome¹⁶⁹. This patient also had myositis, a constellation of conditions more commonly seen with ICI therapy.

Immunotherapies.—ICIs can induce a broad spectrum of immune-related adverse events that differ on the basis of similarities and differences between therapies targeted at cytotoxic T lymphocyte antigen 4 (CTLA4) or at the programmed cell death 1 (PD1)–PD1 ligand 1 (PDL1) axis^{170–172}. The incidence of immune-related adverse events is generally higher with CTLA4 inhibition and highest (>50%) with combined CTLA4 and PDL1 inhibition¹⁷³. Usually, colitis, dermatitis and pneumonitis are the earliest and most common organ

presentations (in descending order, all with incidence of >10%). However, myocarditis, which has been reported with all types of ICIs, is associated with the highest mortality (40% in a 2018 systematic review and meta-analysis)^{174,175}. Precise estimates of the incidence of ICI-induced myocarditis are evolving and expected to rise beyond the currently reported rates of up to 1% with increasing awareness¹⁷⁶. The severest forms of ICI-induced myocarditis are prone to attract clinical attention and encompass decompensated HF, cardiogenic shock and sudden cardiac death. Myocardial biopsy, when performed, is often but not always positive for myocarditis. Sampling bias and sampling error are inherent limitations that confound the conclusions. However, one cannot exclude the possibility that profound, global declines in cardiac function can develop even in the absence of florid myocarditis¹⁷⁷. Furthermore, in one of the first pooled analyses of patients with ICI-induced cardiotoxicity ($n = 30$), late gadolinium enhancement (an indicator of myocardial fibrosis) was seen on cardiac MRI in only 23% of patients and myocardial oedema was seen in only 33% of patients¹⁷⁷. Apical ballooning was diagnosed in 14% of the patients, and among patients with available data on LVEF changes, complete reversibility of LVEF decline was seen in only 50% of them^{138,177}.

By contrast, cardiac function (assessed by echocardiography) remained fairly normal despite evolving fulminant myocarditis with ICI use in the first reported cases of this entity¹⁷⁸. ECG changes, including various forms of conduction block, ventricular ectopy and ventricular tachycardia (VT), and elevation of circulating cTn levels seemed to be more sensitive indicators of myocarditis. Circulating BNP and amino-terminal pro-BNP levels are also recognized as sensitive markers of myocarditis and might even be superior to cTn levels for detecting all forms of ICI-related cardiomyopathy, including those associated with global or regional (apical) cardiac function decline that does not fulfil imaging or tissue criteria for myocarditis^{138,177}. Therefore, at least three different forms of cardiac function abnormalities with putatively different pathological mechanisms can evolve in patients undergoing ICI therapy.

Mechanistically, ICI-induced, immune-related adverse events such as myocarditis can be caused by one or a combination of the following factors: direct binding of ICIs to target molecules on non-lymphocytic cells, with downstream immune activation; formation of new T cells or reactivation of exhausted T cells against tumour antigens that cross-react with off-target tissues; generation of autoantibodies and production of pro-inflammatory cytokines¹³⁶. Interestingly, PD1-deficient mice have a dramatically reduced lifespan that is compensated by cross-breeding with *Rag1*^{-/-} mice, which lack mature B cells and T cells, indicating that an immune mechanism has an important role in the effects of genetic PD1 deficiency¹⁷⁹. Dilated cardiomyopathy was a striking feature and accounted for the premature death of PD1-deficient mice. Although fibrotic reactions were seen sporadically, the ventricular walls of these mice appeared otherwise relatively normal, and scattered degeneration of cardiomyocytes was seen only on electron microscopy, with disarrayed and disrupted myofilaments and irregularly shaped mitochondria throughout the ventricular walls¹⁷⁹. Subsequent studies revealed that the dilated cardiomyopathy was caused by the generation of autoantibodies against cTnI expressed on cardiomyocytes¹⁸⁰. Of interest, tumours in humans can express cTn and other muscle-specific proteins, such as desmin and titin. However, whether the expression of these proteins (and autoantibodies against

them) is causally involved in ICI-related myocarditis (and/or cardiomyopathy) has not been confirmed. PDL1 expression on non-haematopoietic cells, mainly endothelial cells, has an important role in providing protection against cytotoxic T cells^{181–184}. This protection is particularly relevant in the setting of non-self-antigen expression in the heart secondary to a viral infection. The PD1–PDL1 system is also upregulated in the setting of other intrinsic modes of myocardial injury that induce inflammation, such as myocardial ischaemia and MI, probably to prevent inflammatory over-reactivity against cardiac tissue¹⁸⁵. Identifying patients vulnerable to ICI-induced myocarditis (and ICI-related cardiomyopathy) secondary to the upregulation of the PD1–PDL1 system or to other mechanisms is an important current and future need¹⁸⁶.

Management and prevention.—One of the main prerequisites for the appropriate management of ICI-related myocarditis is the knowledge and anticipation of this possible complication. Clinical presentation differs, and subtle signs and symptoms need to be adequately interpreted. Waiting until HF and cardiogenic shock develop to initiate management is suboptimal, especially because any culprit cancer therapy should preferably be discontinued as soon as possible. Management is mainly supportive, which can entail inotropic therapy and even mechanical circulatory support, including extracorporeal membrane oxygenation, as a bridge to recovery, as has been shown in patients who developed fulminant myocarditis with cyclophosphamide and ICIs^{187,188}.

For early detection of cancer therapy-related myocarditis, the standard 12-lead ECG can be very effective. A declining R-wave amplitude (low voltage) can indicate progressive pericardial effusion and loss of myocardial mass, as occurring in haemorrhagic myopericarditis induced by cyclophosphamide. Other ECG indicators of myocardial inflammation include PR interval prolongation, heart block, bradycardia, ventricular ectopy and VT. Biomarkers have a supporting role, and the classic indicator of myocarditis is a protracted period of markedly elevated circulating cTn levels¹⁸⁹. In a retrospective series of 35 patients with ICI-induced myocarditis, circulating cTn and BNP levels were elevated in 33 individuals (94%)¹⁹⁰. However, ECG and cTn levels were an integral element in the diagnostic inclusion of patients in this study, which might explain the high levels of these markers. Of note, in another study on ICI-induced myocarditis and cardiomyopathy, circulating BNP levels were elevated in all patients but cTn levels were elevated in only 46%¹⁷⁷. Coronary angiography is usually performed to exclude CAD leading to MI as the main differential diagnosis. In cases resembling culprit-lesion acute coronary syndrome, cardiac MRI is very valuable to identify acute MI with resolution of epicardial culprit-vessel lesion, acute myocarditis, Takotsubo cardiomyopathy or other cardiomyopathies¹⁹¹. Cardiac positron emission tomography might have a complementary role¹⁹².

In the aforementioned study involving 35 patients with ICI-related myocarditis, dyspnoea and oxygen requirement were two differentiating clinical features between those who developed major adverse cardiac events (MACE; including haemodynamically relevant heart block, cardiac arrest, cardiogenic shock and cardiac-related death) and those who did not¹⁹⁰. Nearly 50% of all patients experienced MACE, with a mortality of 17%. These patients did not receive steroids as quickly or at as high a dosage as patients without MACE. LVEF

was normal in 38% of patients with MACE and in nearly 50% of the patients in the overall cohort.

Immunosuppressive therapies have been recommended for all acutely life-threatening scenarios; that is, with confirmed myocarditis and VT or ventricular fibrillation. Immunosuppressive therapies should also be considered for any other potentially life-threatening presentation, such as advanced conduction disease or heart block owing to presumed myocarditis, pericarditis with cardiac tamponade and acute MI with coronary vasculitis on angiography. Some patients might require a quick escalation of immunosuppressive therapy by including immunoglobulin, antithymocyte globulin, infliximab (if HF is not present), mycophenolate mofetil or tacrolimus¹⁹³. Plasmapheresis has also been implemented, with the goal of accelerating removal of the contributing drug (as well as any potential circulating autoantibodies). This approach is important with ICIs because their half-lives are extremely long: 14.5 days for ipilimumab, 25.0 days for pembrolizumab, 26.7 days for nivolumab and 27.0 days for atezolizumab. Finally, the CTLA4 agonist abatacept might be used in cases of steroid-refractory myocarditis¹⁹⁴. Importantly, the clinical course of ICI-induced myocarditis can be so fulminant that mechanical support such as extracorporeal membrane oxygenation can become necessary and life-saving while all other measures are continued¹⁸⁸. Overall, the hard evidence available at present is insufficient to support any of the anecdotal, albeit reasonable, strategies outlined above, and more evidence-based guidance in this area is needed. Current consensus recommendations by oncology societies are listed in Supplementary Table 2.

Arrhythmias related to cancer therapy

Several rhythm abnormalities can be seen in patients with cancer as they undergo therapy owing to several potential drug–drug interactions, metabolic and electrolyte derangements, and evolving toxic effects. In general, cancer therapy-related arrhythmias can be differentiated into bradycardia and tachycardia, with atrial fibrillation (AF) emerging as an important complication (TABLE 4). The real incidence of cancer therapy-induced arrhythmias is likely to be underestimated because routine cardiac monitoring is often not performed or includes only non-continuous 12-lead ECGs.

Bradycardia

Conventional chemotherapies.—Cardiac arrhythmias were first noted to occur with paclitaxel, more specifically its Kolliphor EL (formerly known as Cremophor EL) formulation, when continuous cardiac monitoring was used to assess hypersensitivity reactions. These paclitaxel-induced arrhythmias are mainly episodes of asymptomatic bradycardia occurring in nearly 30% of patients¹⁹⁵. All other arrhythmias are rare: heart block in 0.1% of patients, supraventricular tachycardia including AF and flutter in 0.2%, and VT and ventricular fibrillation in 0.3%. Most of these arrhythmias are noted with the first or second cycle of paclitaxel therapy, sometimes even within the first 24 h (REF.¹⁹⁶). Typically, these episodes are self-limiting and resolve in 48–72 h after discontinuation of therapy, although brief episodes of supraventricular tachycardia and premature ventricular contractions can persist for up to 1–2 weeks. The mechanisms of paclitaxel-induced

arrhythmias are not precisely defined; for example, whether these phenomena are inherent to paclitaxel or the vehicle used in the Kolliphor EL formulation is not clear.

Another chemotherapeutic classically associated with bradycardia is thalidomide, affecting as many as 50% of all patients with multiple myeloma who were treated with this medication. Elderly patients and those with comorbidities or receiving combination therapies with β -blockers, calcium-channel blockers, digoxin and antiarrhythmic drugs, or exposed to doxorubicin or cyclophosphamide and/or chest radiation therapy are at higher risk of bradycardia. Over-reactivity of the parasympathetic nervous system and thalidomide-induced hypothyroidism have been discussed as potential mechanisms¹⁹⁷.

Targeted cancer therapies.—Sinus bradycardia can be seen with various TKIs (TABLE 4). Among VEGF pathway inhibitors, sinus bradycardia is most common with pazopanib (2–19%) but in a 2018 phase II study¹⁹⁸, grade 4 bradycardia events were reported in 3% of patients with glioblastoma who were receiving bevacizumab in combination with the histone deacetylase (HDAC) inhibitor vorinostat. As in any other patients, other causes of sinus bradycardia in patients with cancer need to be excluded; for instance, sunitinib therapy can cause hypothyroidism, thereby leading to bradycardia¹⁹⁹.

The other class of TKIs that has been associated with risk of bradycardia is ALK inhibitors (BOX 2). Sinus bradycardia has been reported in up to 15% of patients treated with crizotinib and up to 4% of patients treated with ceritinib²⁰⁰. Sinoatrial arrest and asystole have been reported with therapy with ibrutinib, an inhibitor of the tyrosine-protein kinase BTK, in addition to its well-known association with AF and ventricular arrhythmias (see later)²⁰¹.

Immunotherapies.—In patients receiving ICI therapy, bradycardia can be seen in the setting of high degrees of atrioventricular (AV) block^{178,202}. This AV block is secondary to inflammatory infiltration of the myocardium (that is, ICI-associated myocarditis), which can include the AV nodal area and the conduction system in the septum. The extent of AV block can warrant pacemaker implantation, even permanent devices if no resolution occurs in the setting of evolving fibrosis. On the basis of a 2018 systematic review, 10% of the cardiotoxicity events associated with ICI therapy were AV block or conduction disease, which leads to death in 50% of these patients¹⁷⁶.

Radiation therapy.—Bradycardia can develop in patients after radiation therapy as a result of radiation injury and fibrosis in the heart with involvement of the conduction system, including the AV nodal area, the AV and His bundle and bundle branches^{203–205}. In addition, accelerated CAD that affects the sinoatrial artery and the AV nodal branch can contribute to this presentation²⁰⁶. Calcifications of the aortomitral curtain and extensive calcification of the mitral annulus are indicative of the risk of bradycardia^{207,208}.

Management and prevention.—Patients who are at risk of bradycardia with cancer therapy are not well defined but might present with any of the following elements: evidence of pre-existing cardiac conduction abnormalities (bundle branch or AV block); requirement of negatively dromotropic and chronotropic medications (β -blockers, digoxin

and calcium-channel blockers) or antiarrhythmic agents; or poor tolerance of bradycardias. These patients often have underlying ischaemic heart disease, cardiomyopathy or HF. In these patients, chemotherapeutics that have been associated with bradycardia, such as crizotinib, paclitaxel, pazopanib and thalidomide, should be used very carefully, with proper monitoring of heart rate and blood pressure. In the event of symptomatic bradycardia, any potentially contributing medications are to be stopped until its resolution. Thereafter, the risks and benefits of resuming any bradycardia-associated cancer therapy and cardiovascular medications alone or in combination with dose reduction and with or without pacemaker implantation as per the guidelines need to be determined (Supplementary Table 5). Any life-threatening bradycardia requires discontinuation of the cancer therapy unless concurrent medications associated with bradycardia can be discontinued or adjusted in dose (such as a β -blocker and calcium-channel blocker) to allow resumption of the cancer therapy with frequent monitoring (with or without pacemaker support). Electrolytes, especially serum K^+ levels, and renal and thyroid function should be checked. In patients receiving ICI therapy, the development of new conduction disease should prompt an evaluation for the presence of myocarditis.

QTc prolongation and VT

The risk of corrected QT interval (QTc) prolongation has been attributed to the effects of anticancer drugs on the inward current (increase) and outward current (decrease), leading to prolongation of the ventricular action potential, especially the repolarization period. Repolarization is driven by two delayed rectifier K^+ current subtypes, I_{Kr} (rapid) and I_{Ks} (slow), and most drug-induced QTc prolongations are related to blockade of I_{Kr} , which is carried by K^+ voltage-gated channel subfamily H member 2, commonly known as the hERG channel (encoded by *KCNH2*). However, hERG channel blockade might not always translate into QTc prolongation and might not be the sole mechanism.

Conventional chemotherapies.—Arsenic trioxide is a classic agent among conventional chemotherapeutics with the potential to induce QTc prolongation, with up to one third of patients who receive this medication experiencing an increase in the QTc of 30–60 ms from baseline and one third experiencing an increase of >60 ms (REF.²⁰⁹). QTc prolongations of >500 ms can be seen in as many as 65% of patients receiving arsenic trioxide with the use of the Bazett rate correction formula, but in only 24–32% of patients if alternative formulas, such as the Fridericia formula, are used²¹⁰. The latter is preferred in patients with cancer because this formula is associated with less overcorrection at higher heart rates and leads to fewer unnecessary cancer treatment interruptions.

Torsades de pointes is usually not seen with arsenic trioxide therapy unless other contributing factors, such as electrolyte abnormalities, are present²¹⁰. Sudden cardiac death has been reported but is extremely rare. Mechanistically, arsenic trioxide can block both I_{Kr} and I_{Ks} but activates the ATP-dependent K^+ current I_{K-ATP} (REF.²¹¹). Other conventional chemotherapeutics with the potential to induce QTc prolongation include oxaliplatin, which increases the inward Na^+ current²¹¹. For drugs such as paclitaxel, docetaxel and 5-FU, induction of myocardial ischaemia might be another potential mechanism leading to QTc prolongation.

Targeted cancer therapies.—TKIs have a heterogeneous effect on QTc: on average, a 15-ms increase from baseline but notably more for sunitinib, lapatinib, nilotinib and vandetanib (on average, increases of 22.4, 23.4, 25.8 and 36.4 ms, respectively, from baseline)¹⁹⁷. Although the incidences can differ considerably, in patients receiving TKIs, including dasatinib, nilotinib, pazopanib and sunitinib, QTc prolongations to 500 ms were noted in <5% of patients and ventricular arrhythmia and sudden cardiac death were noted in <1% of patients²¹². Vandetanib is the drug with the most robust evidence by the number of studies, and the incidence of all-grade or high-grade QTc prolongation with vandetanib is 16.4% and 3.7%, respectively, among patients with non-thyroid cancer and 18% and 12%, respectively, among patients with thyroid cancer, who have longer durations of treatment¹⁹⁷.

A systematic, registry-based study published in 2018 confirmed the reports on the risk of ventricular arrhythmias with ibrutinib^{213–218}. On the basis of the Naranjo Adverse Drug Reaction Probability Scale score, the association of ibrutinib with ventricular arrhythmias was deemed to be at least probable, and overall a more than 10 times higher than expected rate of VT was observed. Of note, VT and ventricular fibrillation, even polymorphic VT, has been reported with ibrutinib treatment even in the presence of a normal QTc²¹⁸. AF remained a predictor of VT in the adjusted analyses. In mice, atrial and ventricular arrhythmias were seen even after a single dose of ibrutinib, and high serum concentrations of ibrutinib, rather than chronicity of the treatment, seems to be the determining factor²¹⁹.

HDAC inhibitors (BOX 2) have also been associated with QTc prolongation and arrhythmias¹⁹⁷. QTc prolongation can be seen in 10% of patients receiving the HDAC inhibitor romidepsin, supraventricular tachycardia can be seen in 38%, VT can be seen in 14%, atrial ectopy can be seen in 65% and ventricular ectopy can be seen in 38%. Both QTc prolongation and arrhythmias usually resolve before the next cycle of therapy. However, cases of sudden cardiac death have been reported with the use of romidepsin, underscoring the need for vigilance. QTc prolongation has also been reported in 10% of patients receiving dacinostat, 6.3–28.0% of patients receiving panobinostat and 3.5–6.0% of patients receiving vorinostat²¹². These observations are consistent with a class effect, and blockade of the hERG channel by HDAC inhibitors has been proposed as a mechanistic explanation. The risk of QTc prolongation increases as a function of peak dose; that is, it is highest with short bolus administrations. The risk of torsades de pointes is higher in women, elderly patients and patients with bradyarrhythmias, electrolyte abnormalities, structural heart diseases or baseline QTc prolongation.

Inhibitors of the cyclin-dependent kinases CDK4 and CDK6 (BOX 2) are another class of drug that has been associated with QTc-prolonging potential, albeit with great variations in the associated risk²²⁰. Ribociclib is the drug associated with the highest risk, and QTc prolongation is seen in a concentration-dependent manner, usually within the first 4 weeks of treatment, and the ECG changes are reversible with therapy interruption. In clinical trials, 6% of patients with advanced or metastatic breast cancer who were treated with ribociclib (in combination with an aromatase inhibitor or fulvestrant) had a >60-ms increase in QTc from baseline, and 1% had a QTc of >500 ms (REF.²²¹). No cases of torsades de pointes were reported but one sudden cardiac death (0.3%) occurred in a patient with concomitant hypokalaemia²²². Ribociclib should not be combined with tamoxifen given the

nearly threefold higher incidence of QTc increase (by >60 ms) than that seen with single therapy. Palbociclib and abemaciclib do not seem to lead to clinically significant (increase of >60 ms or duration >500 ms) QTc prolongations²²³.

Immunotherapies.—In patients receiving ICIs, ventricular arrhythmias might be a result of the inflammatory infiltration of the myocardium¹⁷⁸. Ventricular arrhythmias are seen in 5–10% of patients receiving ICIs and are associated with 40% mortality¹⁷⁶. Similarly to new-onset conduction disease, ventricular arrhythmias indicate a more complicated clinical course and should prompt investigations into the presence of myocarditis. Ventricular arrhythmias could also conceivably be seen with other forms of cardiomyopathy reported with ICI therapy.

Radiation therapy.—Despite the ample reports on cardiac fibrosis in patients who underwent radiation therapy involving the chest, reports of ventricular arrhythmia are scarce. Indeed, cardiac radiation therapy is being explored as an alternative to invasive ventricular ablation in the treatment of ventricular arrhythmia²²⁴. In survivors of childhood cancer, some studies indicate a 3–5% incidence of VT, but incidence rates differ by treatment: 4% among those treated with chest radiation therapy and 8% among those treated with both chest radiation therapy and anthracyclines²²⁵. Importantly, ventricular arrhythmias are not restricted to patients with cardiac dysfunction and can be noted even in those with preserved LVEF²²⁵.

Management and prevention.—Patients with cancer who have ECG abnormalities, impaired exercise capacity or cardiovascular diseases at baseline should be assumed to be more susceptible to cancer therapy-induced arrhythmias, as are those undergoing treatment regimens with known cardiotoxicity potential. Therefore, as a general rule, comorbidities that could represent a possible arrhythmogenic substrate should be identified and treated aggressively before and during cancer therapy. Early identification and appropriate management of cardiac ischaemia, dysfunction and remodelling is also likely to be the best strategy to modulate the arrhythmogenic substrate and improve outcomes in patients with cancer therapy-induced arrhythmias. These recommendations hold true for QTc prolongation and related ventricular arrhythmias.

Crizotinib, dasatinib, lapatinib, nilotinib, pazopanib, sorafenib, sunitinib, vandetanib and vemurafenib should be administered with caution in patients with pre-existing QTc prolongation or QTc prolongation-related risk factors including medications and drug–drug interactions. As illustrated for several TKIs, such as vandetanib, electrolyte levels should be corrected before initiation of cancer therapy (the goal value for serum K⁺ levels is 4 mEq/l to the upper limit of normal and for serum Mg²⁺ and serum Ca²⁺ levels within the normal range) and should be monitored along with serial ECGs, as outlined earlier (at baseline, at 2–4 weeks, at 8–12 weeks and every 3 months thereafter). The same frequency of monitoring is required after dose reductions or therapy interruptions of more than 2 weeks. Importantly, vandetanib has a half-life of 19 days and, therefore, any adverse reactions can resolve slowly. The upper limit for QTc with vandetanib therapy is 450 ms before the start of therapy and 500 ms during therapy. If these thresholds are surpassed, therapy should be stopped and might be resumed at a reduced dose. With nilotinib therapy, ECGs should

be taken 7 days after initiation or change of therapy, and any QTc >480 ms requires a temporary cessation of therapy (or permanent cessation if QTc prolongation is recurrent after measures have been taken) until QTc is 450–480 ms (then therapy should be resumed at half the dose) or <450 ms (then therapy should be resumed at the full dose). Any grade 4 (that is, life-threatening) QTc event also precludes any further cancer therapy. Ventricular arrhythmias should be managed as usual according to clinical guidelines²²⁶ (Supplementary Table 6).

Atrial fibrillation

AF in patients with cancer has been reported for more than half a century, initially as a consequence of neoplastic infiltration or mechanical pressure on the heart or as a complication of oncological thoracic surgery or medical therapy. Subsequently, a bidirectional and more so multifactorial association between cancer and AF was recognized. For instance, the Women's Health Study²²⁷ showed that the risk of cancer was threefold higher in the first 3 months after diagnosis of AF and remained elevated by 42% beyond the first year. Conversely, the risk of AF was found to be increased by 20% in the first 3 months after cancer diagnosis²²⁷. The exact mechanisms underlying this association are not defined, in particular, how AF begets cancer. One possible explanation is that anticoagulant use for treatment of AF unmasks the presence of malignancies by the induction of bleeding events in the tumour²²⁸. Cancer antigen 125 (also known as MUC16) is not only a marker for tumours, such as in ovarian cancer, but is also a predictor of AF in postmenopausal women²²⁹. Shared risk factors in AF and cancer include obesity and inflammation. Whether AF in patients with cancer can occur without any underlying substrate and predisposition is not fully clear. Patients with cancer are usually not fully characterized in terms of atrial filling pressures and pre-existing remodelling dynamics. General precipitating and aggravating factors for AF in patients with cancer include cardiac masses or infiltration, sympathetic stressors, acute and chronic inflammation, pericarditis, mediastinal irradiation, surgery, bone marrow transplantation and chemotherapy²³⁰.

Conventional chemotherapy.—As outlined in TABLE 4, AF has been reported with numerous traditional chemotherapies, especially with melphalan and paclitaxel. The precise mechanisms of melphalan-related supraventricular tachycardia are not known. AF is seen in 8% of patients receiving melphalan, and is more common in elderly patients and in those with reduced renal function or hypertension²³¹. Left atrial enlargement and particularly a history of AF are predictive of the risk of AF in patients receiving melphalan²³¹. A history of cardiovascular disease has also been considered to be a risk factor for AF in patients receiving paclitaxel, but AF can occur in the absence of risk factors for AF. The incidence of paclitaxel-related AF is <2%²³².

Targeted cancer therapy.—A renaissance of the topic of AF and cancer has occurred with the use of the TKI ibrutinib²³³. Incidence rates of AF with the use of ibrutinib range from 3% to 16% (on average 8%) according to a systematic review published in 2017 (REFS^{234,235}). A risk prediction model for AF in patients with chronic lymphocytic leukaemia was developed at the Mayo Clinic and externally validated²³³. The variables included in this model include age (<65 years, 65–74 years and >74 years), sex, valvular

heart disease and hypertension²³³. The score categories are 0–1, 2–3, 4 and 5+, and each step up in category corresponds to a doubling of the risk of AF (zero, twofold, fourfold and eightfold increase). The predictiveness of this model for AF in patients receiving ibrutinib was confirmed, as was the Framingham model and a model by Visentin et al. (the latter potentially performing the best)^{236,237}. Other studies are in general agreement with the concept that patients who develop AF with exposure to ibrutinib have either a history of AF or predisposition for AF^{238,239}. The underlying mechanisms are not clear but might be related to suppression of phosphoinositide 3-kinase (PI3K)–AKT pathway activity in cardiomyocytes^{201,240}. The PI3K–AKT pathway is regulated by BTK and the tyrosine-protein kinase TEC, both targets of ibrutinib^{201,241}. The second-generation BTK inhibitor acalabrutinib neither increases the risk of AF and bleeding nor inhibits TEC and SRC family members as ibrutinib does^{242,243}.

Immunotherapy.—Inflammation and AF have been linked but with debated causality (direct, indirect or not at all)^{244–246}. Nevertheless, patients with higher levels of C-reactive protein (CRP) in the plasma have more AF episodes, and baseline plasma CRP levels are predictive of future risk of AF²⁴⁷. Not surprisingly, new-onset AF has been seen in patients receiving CAR T cell therapy, even in very young patients and those without a history of AF^{123,248}. AF has also been reported with ICI therapy^{249,250}. AF in this setting could be caused by the induction of pericarditis or cardiomyopathy. Other conditions induced by ICIs that can contribute to AF include, for instance, thyroiditis.

Radiation therapy.—AF can develop in the setting of pericarditis or as a consequence of the development of restrictive cardiomyopathy in patients who have under-gone radiation therapy. Nevertheless, a history of HF is less common in patients with cancer who have under-gone chest radiation therapy and develop AF than in the general AF population²⁵¹. Some studies even concluded that the risk of AF is not overall higher in this patient population than in the general population. As with VT, radiation therapy is now being tested as a non-invasive ablative strategy for AF treatment²⁵².

Management and prevention.—The principles and goals of the management of AF in patients with cancer are generally the same as those in the general population (Supplementary Table 7), albeit with some important differences (FIG. 3). The first goal is to control heart rates with a lenient target with the use of β -blockers, Ca^{2+} channel blockers and digoxin. If this strategy does not suffice and patients remain symptomatic, for example, with palpitations, dyspnoea and effort intolerance, antiarrhythmic drugs can be used. In patients with cancer who are actively receiving cancer therapy, various drug–drug interactions can be a complicating factor for any such interventions. This complication particularly exists for multitargeted TKIs.

An illustrative example in this regard is ibrutinib, which can increase the plasma levels of amiodarone, carvedilol, digoxin, diltiazem and verapamil²⁵³. Conversely, amiodarone and the calcium-channel blockers diltiazem and verapamil can increase the plasma levels of ibrutinib severalfold by interfering with the hepatic metabolism of ibrutinib through inhibition of cytochrome P450 3A4 (CYP3A4)²⁵³. Therefore, the β -blockers atenolol and metoprolol should be used as first-line agents²⁵³. Class Ib (mexiletine) and class Ic

(flecainide and propafenone) drugs and sotalol might be valid choices for antiarrhythmic drug therapy, depending on cardiovascular comorbidities. If needed in patients with HF, amiodarone and digoxin should be used very carefully (as substrates of P-glycoprotein, which is inhibited by ibrutinib; amiodarone is also an inhibitor of P-glycoprotein and a major CYP3A substrate); dronedarone should not be used (as a moderate CYP3A4 inhibitor and a major CYP3A4 substrate). More than two thirds of patients with AF who are receiving ibrutinib might not experience long-term success with cardioversion, suggesting that antiarrhythmic therapy should be started even when cardioversion is considered²³⁹. The role of ablation in patients with cancer and AF is currently not defined, especially as a first-line therapy to avoid potentially fatal drug–drug interactions. If at all possible, ibrutinib therapy should not be discontinued but instead the dose should be reduced because no significant difference in the rate of AF resolution with the two strategies has been observed, whereas ibrutinib therapy discontinuation leads to a significantly (about twofold) higher risk of cancer progression²³⁹. A systematic review did not find a relationship between ibrutinib dose and the occurrence of either AF or bleeding²³⁵.

Anticoagulation therapy in patients with cancer can be problematic in general and especially in patients receiving ibrutinib because they are predisposed to bleeding (60% incidence in single-group studies, 44% in randomized clinical trials, with high-grade haemorrhage in up to 7% of patients)²⁵⁴. Ibrutinib has a unique antiplatelet effect, inhibiting mainly von Willebrand factor and collagen-mediated platelet activation (in addition to fibrinogen-activated platelet activation), which could be very effective in the setting of atherosclerotic plaque rupture^{255,256}. Importantly, these activation pathways are distinct from those inhibited by aspirin (cyclooxygenase) and thienopyridines (ADP receptor), and combination therapy would lead to a profoundly additive effect and bleeding risk; therefore, this strategy is not recommended. The combination of any antiplatelet agent with anticoagulation therapy increases the risk of bleeding by default. In terms of drug–drug interactions, the adverse potential is not deemed very high for the combination of ibrutinib and warfarin, which together with the option of warfarin reversal has favoured the use of warfarin in patients receiving ibrutinib therapy²⁴¹. However, wide fluctuations in the international normalized ratio can be seen in patients receiving ibrutinib and warfarin, and although warfarin was allowed initially in clinical trials, the trial criteria were later amended to exclude patients receiving warfarin because of excessive bleeding events²⁵⁶. Low-molecular-weight heparin has therefore often been a preferred choice for anticoagulation in these patients (especially in those with normal renal function). Nevertheless, the costs and discomfort of the injections remain major disadvantages of using low-molecular-weight heparin, especially considering the chronicity of this treatment. Direct oral anticoagulants have emerged as an attractive alternative, even in patients with cancer and AF^{257–262}. Given the inhibitory action on P-glycoprotein, ibrutinib has the potential to increase the serum levels of all direct oral anticoagulants, especially dabigatran and edoxaban and, to a lesser degree, apixaban and rivaroxaban²⁶³. Indeed, no grade 3 bleeding events were noted in 18 patients who developed AF with ibrutinib therapy, seven of whom were treated with apixaban²⁶⁴. Anticoagulation therapy in patients receiving ibrutinib should be for the duration of the increased risk of AF, which is certainly for the duration of ibrutinib therapy. However, these patients might be at high risk of AF regardless of receiving ibrutinib^{233,238}. For patients with malignancies in

general, an approach that is based on the stage within the continuum of cancer care might be advisable (BOX 5).

Importantly, when choosing the anticoagulation strategy, the CHA₂DS₂-VASc score seems to perform the same in patients with cancer as in patients without cancer for those with baseline AF^{265–267}. However, the CHA₂DS₂-VASc score does not account for cancer-induced hypercoagulability and does not perform as well for patients who newly develop AF during cancer therapy^{268–270}. With regard to bleeding risk prediction, differences in patients with cancer are also not included in the HAS-BLED score and, for this reason, this score might not perform ideally in patients with cancer either²⁶⁵. These difficulties might explain why, at least in the USA, patients with cancer take medications for anticoagulation at a much lower rate than patients without cancer, despite deriving the same benefit²⁷¹. Intriguingly, involvement of a cardiologist markedly improved this management aspect²⁷¹.

In terms of primary prevention, how to identify patients with cancer at high risk of AF accurately and whether they should be prophylactically treated with antiarrhythmic drugs is currently unknown. These are pertinent questions especially for those patients with cancer whose treatment course can be greatly affected in a negative manner by the development of AF (for example, those undergoing bone marrow transplantation or CAR T cell therapy or responders to long-term therapy with ibrutinib).

Conclusions

Cancer therapy has evolved remarkably over the decades, from chemical therapeutics to targeted molecular therapies and, most recently, immunotherapies. With these developments, the cardiovascular toxicity profile of cancer therapeutics is broadening. Although familiarity with the old concepts and management recommendations has to remain, one has to be attentive to new concepts and discoveries in cardio-oncology. This multidisciplinary area will gain importance in the years to come, with the ageing of the general population and the consequent increase in the incidence and prevalence of both cancer and cardiovascular diseases. Although this Review focuses on the active therapy phase in patients with cancer, the continuum of care should not be forgotten. Some patients will need to be evaluated before and continued to be followed up for cardiovascular risks after exposure to the therapies discussed in this Review. In addition to cardiotoxicity, vascular toxicity and arrhythmias associated with cancer therapies are important topic areas for every cardiologist to know given the potential for fatal outcomes. Finally, in view of the improving survival rates in patients with cancer, how cardiovascular diseases and cardiovascular toxicities of cancer therapies are managed in these patients will become increasingly important.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- Cancer therapy has evolved from the administration of chemical compounds and radiation therapy to the use of targeted agents and immunotherapies.
- Along with these developments, the cardiovascular toxicity spectrum of cancer therapies has been changing but cardiac toxicity remains of greatest concern.
- Inflammatory and immune mechanisms have to be taken into account when considering cardiotoxicity in patients receiving immune checkpoint inhibitor or chimeric antigen receptor T cell therapies.
- With the newer cancer therapies, atrial fibrillation is emerging as the most relevant and practically challenging arrhythmia in patients with cancer.
- Corrected QT interval prolongation, ventricular arrhythmias and cardiac arrest can also occur with many of the newer targeted agents.

Box 1 |**Proposal for a pathophysiology-based classification of cancer therapy-related cardiomyopathies**

A decline in cardiac function in patients with cancer can occur as a consequence of direct toxic effects of cancer therapies on the myocardium (primary or type I cardiomyopathy) or secondary to other alterations that translate into a reduction in cardiac function (secondary or type II cardiomyopathy). Non-toxic or non-reactive primary inflammatory myocarditis is a unique subtype of cancer therapy-related cardiomyopathy (type III), and requires immunosuppressive treatment. In type II scenarios, treatment of the underlying or contributing abnormality (such as coronary or valvular heart disease) is crucial to the restoration of cardiac function, whereas for type I scenarios, heart failure therapy is essential. The table shows the cancer therapies that have been associated with each type of cardiomyopathy, as well as the diagnosis and management strategies.

Characteristic	Cancer therapy-related cardiomyopathy		
	Type I	Type II	Type III
Definition	Direct impairing effect on the myocardium	Indirect impairing effect on the myocardium	Impairing effect owing to myocarditis
Risk with cancer therapy			
Doxorubicin	Yes	Yes	Yes (toxic or reactive)
Cyclophosphamide	Yes	Yes	Yes (toxic or reactive)
5-Fluorouracil	Yes	Yes	NR
HER2 (ERBB2) inhibitors	Yes	Unclear	NR
VEGF inhibitors	Yes (TKIs)	Yes	Unclear
ICIs	Possible	Possible	Yes (immunomediated)
Radiation therapy	Yes (at high dose)	Yes	Yes (toxic or reactive)
Diagnosis			
Imaging	Echocardiography, cardiac MRI, MUGA scan	(Stress) echocardiography, (stress) cardiac MRI, nuclear stress test, CT coronary angiography, vasoreactivity studies	Cardiac MRI, PET, echocardiography
Biomarkers	Cardiac troponins, natriuretic peptides (especially long term)	Thyroid function studies, cytokines, catecholamines ECG abnormalities (e.g. ST-segment shifts, T-wave inversions)	Cardiac troponins, natriuretic peptides, ECG abnormalities (e.g. heart block, ectopy)
Management			
Treatment	Stop cancer therapy, β -blocker(carvedilol), ACE inhibitor, ARB, spironolactone	Stop cancer therapy, therapy directed at the underlying cause (e.g. correction of myocardial ischaemia or valve disease)	Stop cancer therapy; for ICI therapy, anti-inflammatory and immunosuppressive therapy, supportive care as needed (e.g. ECMO)

Characteristic	Cancer therapy-related cardiomyopathy		
	Type I	Type II	Type III
Prevention	Screening for and optimal treatment of comorbidities, exercise; for anthracyclines, cardiovascular medications (carvedilol or nebivolol, ACE inhibitor, ARB or spironolactone, statins, dexrazoxane)	Screening for and optimal treatment of predisposing conditions, dose and type of administration; for radiation therapy, dose reduction (e.g. shielding, positioning or proton beam)	Screening for and optimal treatment of comorbidities (efficacy not proven), early detection with biomarkers

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; ICI, immune checkpoint inhibitor; MUGA, multigated acquisition; NR, not reported; PET, positron emission tomography; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Box 2 |**Targeted cancer therapies****ALK inhibitors**

ALK is an oncogene encoding a protein involved in cell growth. Mutated forms of the *ALK* gene and protein have been found, for instance, in non-small-cell lung cancer and anaplastic large-cell lymphoma, in which *ALK* inhibitors are used.

BRAF inhibitors

The serine/threonine-protein kinase *BRAF* is a member of the *RAF* family and a downstream target of *RAS* in the mitogen-activated protein kinase (*MAPK*) signalling pathway. Activating mutations in *BRAF* have been described in a few cancers, such as V600E in melanoma and non-small-cell lung cancer. *BRAF* inhibitors can be combined with *MAPK/ERK* kinase (*MEK*) inhibitors to extend the time to resistance and the tumour and survival responses.

CDK inhibitors

Cyclin-dependent kinases (*CDKs*) phosphorylate and thereby regulate the activity of proteins that are important for progression through the cell cycle and cell division. *CDK4* and *CDK6* inhibitors are used to interrupt this action and thereby the proliferation of cancer cells, which are more likely to have disturbances in *CDK4* and *CDK6*, such as hormone receptor-positive breast cancer cells.

EGFR and HER2 inhibitors

The four main members of the human epidermal growth factor receptor (*EGFR*) family, *EGFR* (also known as *HER1*), *HER2* (also known as *ERBB2*), *ERBB3* (also known as *HER3*) and *ERBB4* (also known as *HER4*), regulate the growth, survival and differentiation of various cells via multiple intracellular signal transduction pathways after ligand-mediated association of two receptors (dimerization). *HER2*-directed therapy is extremely important in breast oncology and includes drugs that inhibit the extracellular domains (pertuzumab and trastuzumab) or the intracellular tyrosine kinase domain (lapatinib) of the receptor. Inhibitors targeting the tyrosine kinase domain of *EGFR* (such as erlotinib) are used in lung oncology.

HDAC inhibitors

Histone deacetylase (*HDAC*) inhibitors interfere with the actions of *HDACs*, which are enzymes involved in the remodelling of chromatin and have an important role in the epigenetic regulation of gene expression and the regulation of the activity of non-histone proteins through hypoacetylation. These drugs are approved by the *FDA* for use in T cell lymphoma and myeloma.

MEK inhibitors

The classic *MAPK* signalling pathway is important for cell growth and division. This pathway is activated, for example, by growth factors such as *EGF*, and entails the sequential activation of *RAS*, *RAF*, *MAPK/ERK1* (*MEK1*), *MEK2*, *ERK1* and *ERK2*.

Aberrant activation occurs through gain-of-function mutations in *RAS* and *RAF* gene family members, which are among the most frequently mutated genes in human cancer. MEK inhibitors lock non-phosphorylated MEK1 and MEK2 into a catalytically inactive state that is not related to the ATP-binding pocket of the proteins, which reduces the risk of off-target effects. These drugs are used primarily in patients with melanoma.

MET

MET is a receptor tyrosine kinase that, after binding with its ligand, hepatocyte growth factor, activates the MAPK and other intracellular signalling pathways involved in cell proliferation, motility, migration and invasion. Overactivation of MET via mutation, amplification or protein overexpression has been documented in various human malignancies. MET inhibitors interfere with the tyrosine kinase activity of MET and are approved for use in patients with thyroid, renal cell or hepatocellular cancer.

mTOR inhibitors

Mechanistic target of rapamycin (mTOR) is a protein kinase that forms two types of mTOR complexes (mTORC). mTORC1 suppresses catabolic processes (such as autophagy) and activates anabolic pathways (such as protein synthesis), thereby supporting cell growth. mTOR inhibitors inhibit mTORC1, thereby shifting cancer cell metabolism to a status unfavourable for cell growth. These drugs are prescribed for patients with renal cell cancer or breast cancer.

Topoisomerase inhibitors

As polymerases separate DNA strands for transcription of gene information or duplication, the remaining portions of the DNA strands become more densely coiled. Topoisomerases cleave and relax hypercoiled DNA segments and subsequently reattach the cleaved ends. On the basis of their cleaving either one or both strands of DNA, topoisomerases are designated as type I or type II, respectively, and so are their inhibitors. Topoisomerase inhibition leads to the formation of irreversible covalent crosslinks between topoisomerases and DNA, thereby stalling DNA expression, duplication and integrity.

VEGF inhibitors

Vascular endothelial growth factors (VEGFs) have an important role in the formation of new vessels (angiogenesis), thereby supporting tumour growth and metastasis. VEGF inhibitors interfere with this aspect of tumour growth and bind to VEGFA (bevacizumab), trap VEGF subtypes (aflibercept), bind to VEGF receptor 2 (VEGFR2) (ramucirumab) or inhibit VEGFR2 tyrosine kinase activity (pazopanib, sorafenib and sunitinib). These agents are indicated for patients with renal cell cancer or thyroid cancer.

Box 3 |**CAR T cell therapy**

T cells are normally activated when the T cell receptor (TCR) recognizes an antigen that is presented in conjunction with MHC class I or class II complexes. By contrast, engineered chimeric antigen receptors (CARs) recognize the antigen in a manner similar to that of an antibody, in an MHC-unrestricted manner. CARs consist of an extracellular antigen-recognition domain (most commonly a monoclonal antibody single-chain variable region that targets a tumour-associated antigen) linked to a T cell signalling transmembrane domain (such as an intracellular fragment of the TCR CD3 ζ chain in 'first-generation' CARs) that anchors the chimeric receptor in the cell membrane and activates the T cell when the extracellular portion recognizes the target cell expressing the specific antigen, thereby linking recognition to activation. Activation is mediated by the intracellular fraction, which stimulates T cell proliferation, cytokine secretion and cytolysis to eliminate the target cell. Therefore, expression of engineered CARs on T cells allows for the control of T cell targeting of tumour cells with high degree of specificity. To generate CAR T cells, T cells are harvested from the patient (or from an allogeneic donor) and are transfected with a gene-therapy vector (such as a lentivirus) encoding the CAR construct.

The first CAR T cell strategy that was developed targeted melanoma-associated antigen 3 (MAGEA3), the first human tumour-associated antigen to be specifically recognized by CD8⁺ T cells. Another asset in favour of this approach was the expression of MAGEA3 in a wide variety of neoplasms, particularly melanoma and non-small-cell lung cancer, but not in normal tissues except the testes and placenta (where this antigen is not presented to CD4⁺ T cells and CD8⁺ T cells).

HER2 (also known as ERBB2 or neu) was chosen early on as another promising tumour-associated antigen target for CAR T cells. The hope was for the broader application of this approach as a therapeutic strategy for all cancers expressing HER2, including breast, gastric, colon, renal and ovarian cancer. By contrast, CD19 was chosen as a target for CAR T cell therapy because its expression is confined to B cells and the levels are much higher than those of any other markers in B cell leukaemias and lymphomas. Furthermore, any potential depletion of B cells that might arise as a consequence of the anti-CD19 CAR T cell therapy was thought to be beneficial to avoid any potential antibody response to the engineered CAR T cells.

Box 4 |**Immune checkpoint inhibitors**

T cell activation is modulated not only by co-stimulation but also co-inhibition pathways to prevent an excessive immune response. These pathways can be exploited by tumour cells to escape immune-mediated destruction. Immune checkpoint inhibitors (ICIs) are molecules that target T cell inhibition pathways, such as the cytotoxic T lymphocyte antigen 4 (CTLA4) and programmed cell death 1 (PD1) pathways, thereby reversing the immune tolerance of the T cells towards tumour cells and promoting T cell antitumour activity.

CTLA4, the first target used for clinical ICI therapy, interacts with the same surface molecules on antigen-presenting cells that interact with the co-stimulatory signal CD28: CD80 and CD86. CTLA4 directly competes with CD28 for the binding sites, but with much higher affinity. In contrast to the signalling of CD28 promoting T cell activation, CTLA4 signalling blocks the T cell response. CTLA4 is stored in intracellular vesicles in the T cell, which are transported to the cell surface on antigen-driven engagement of the T cell receptor. This relocation usually occurs within 2 days of T cell activation and affects both CD4⁺ T cells and CD8⁺ T cells in the lymphatic tissues. Therefore, antibodies interfering with CTLA4 are directed to T cells that interact with antigen-presenting cells in lymphoid organs in the early stage of the adaptive immune response and, most of all, to T helper cells. In addition, CTLA4 is constitutively expressed and has a vital role in regulatory T cells. Therefore, CTLA4 inhibition has a profoundly negative effect on this anti-inflammatory T cell population.

The immune checkpoint that became the second and more prevalent target for clinical therapy is the PD1–PD1 ligand 1 (PDL1) system. This pathway is a negative regulator of T cell activity in peripheral tissues, including tumours. PD1 is expressed in all inflammatory cells, including monocytes, dendritic cells, natural killer cells, B cells and T cells. In the tumour, PD1 is expressed in activated tumour-infiltrating (mainly CD4⁺) T cells. In addition, PD1 is highly expressed on regulatory T cells, which also tend to infiltrate tumours densely. PDL1, which triggers the inhibitory signal in these immune cells on binding to PD1, is expressed by various tissue and cancer cells, as well as by tumour-infiltrating macrophages. Antigen-presenting cells also express PDL2, another ligand for PD1 with functions overlapping those of PDL1.

Box 5 |**Anticoagulation strategies in patients with cancer and atrial fibrillation**

In the absence of clinical trial data, safety concerns guide decision-making regarding the anticoagulation regimen for patients with cancer and atrial fibrillation, assuming that all strategies have equal efficacy to prevent thromboembolism. On the basis of the factors outlined in the table, a reasonable approach would be to use either vitamin K antagonists (VKAs) or non-vitamin K antagonist oral anticoagulants (NOACs) before and after active cancer therapy, when steady-state conditions are reached (that is, no major changes in drug regimen, renal and liver function, and blood counts and coagulation status are expected). During active cancer therapy, low-molecular-weight heparin (LMWH) might be the preferred choice.

Anticoagulant regimen	Preferred timing with respect to cancer therapy	Drugs and dosing	Reversibility	Drug-drug interactions	Reduced renal function	Reduced liver function	Cost	Comments
VKAs	Before and after	Coumadin, dosing according to INR	Vitamin K, fresh frozen plasma or prothrombin complex concentrate	+++	Preferred if severe end-stage renal disease without haemodialysis	Not required	Low	Inconvenience owing to the need for recurrent INR checks
LMWH	During	Enoxaparin 1 mg/kg subcutaneously twice daily; dalteparin 200 U/kg subcutaneously daily	Protamine (but unlike with unfractionated heparin, it does not completely abolish the anti-factor Xa activity of LMWH)	+	Caution if eGFR <30 ml/min; monitor factor Xa levels	Not required	High	Heparin-induced thrombocytopenia; discomfort with injections; challenging long-term treatment
NOACs	Before and after	Rivaroxaban 20 mg orally daily; endoxaban 60 mg orally daily; dabigatran 150 mg orally twice daily; apixaban 5 mg orally twice daily	Idarucizumab (Praxbind) for dabigatran; andexanet alfa (Andexxa), if available, for apixaban or rivaroxaban; or four-factor prothrombin complex concentrate for all other NOACs	+++	Reduce rivaroxaban dosage to 15 mg daily; reduce endoxaban dosage to 30 mg daily if eGFR is 15–50 ml/min; reduce dabigatran dosage to 75 mg twice daily if eGFR is 15–30 ml/min; reduce apixaban dosage to 2.5 mg twice daily if serum creatinine level is 1.5 mg/dl and either age 80 years or	Not recommended with moderate-to-severe (rivaroxaban and endoxaban) or severe (apixaban) liver dysfunction (Child-Pugh class B/C and class C)	High	Lack of ample experience and publications in patients with cancer; concerns for use in patients with gastrointestinal (and genitourinary) tract lesions

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Anticoagulant regimen	Preferred timing with respect to cancer therapy	Drugs and dosing	Reversibility	Drug-drug interactions	Reduced renal function	Reduced liver function	Cost	Comments
					weight 60 kg			
egFR, estimated glomerular filtration rate; INR, international normalized ratio.								

	Arrhythmia	Cardio-myopathy	Arterial vascular disease	Venous thrombo-embolism	Pulmonary hypertension	Systemic hypertension	Pericardial disease	Valvular heart disease
Conventional chemotherapies								
Anthracyclines (doxorubicin, epirubicin)		✓						
Alkylating agents (cyclophosphamide, melphalan)	✓	✓	✓					
Antimetabolites (5-fluorouracil, capecitabine, cytarabine)		✓	✓				✓ Cytarabine	
Microtubule-binding agents (paclitaxel)	✓		✓					
Platinum-based therapy (cisplatin)			✓	✓		✓		
Antibiotic (bleomycin)			✓		✓			
Immunomodulatory drugs (thalidomide)	✓			✓				
Targeted agents								
Proteasome inhibitors (bortezomib, carfilzomib)		✓	✓			✓		
HDAC inhibitors (vorinostat)	✓							
CDK4/CDK6 inhibitors (ribociclib)	✓							
mTOR inhibitors (everolimus)	✓	✓	✓	✓		✓		
HER2 inhibitors (pertuzumab, trastuzumab)		✓						
VEGF inhibitors (bevacizumab, sunitinib)		✓	✓	✓		✓		
BCR-ABL1 inhibitors (dasatinib, nilotinib, ponatinib)	✓		✓	✓	✓ Dasatinib			
BTK inhibitors (ibrutinib)	✓							
ALK inhibitors (alectinib, ceritinib, crizotinib)	✓				✓			
BRAF inhibitors (dabrafenib)	✓	✓						
MEK inhibitors (binimetinib, cobimetinib, trametinib)	✓	✓			✓			
Immunotherapies								
Immune checkpoint inhibitors	✓	✓	✓	✓	✓		✓	
CAR T cell therapy	✓	✓	✓	✓	✓		✓	
Other therapies								
Radiation therapy	✓	✓	✓		✓		✓	✓

Fig. 1 |. Outline of cardiovascular toxic effects associated with cancer therapies.

Numerous cancer therapies have been associated with adverse effects and complications across the entirety of the cardiovascular system. As illustrated, some therapies have a very confined and others have a very broad cardiovascular toxicity profile. Classic chemical compounds are shown in blue, targeted therapies are shown in pink, immunotherapies are shown in purple and radiation therapy is shown in green. CAR, chimeric antigen receptor; HDAC, histone deacetylase; MEK, MAPK/ERK kinase; mTOR, mechanistic target of rapamycin; VEGF, vascular endothelial growth factor.

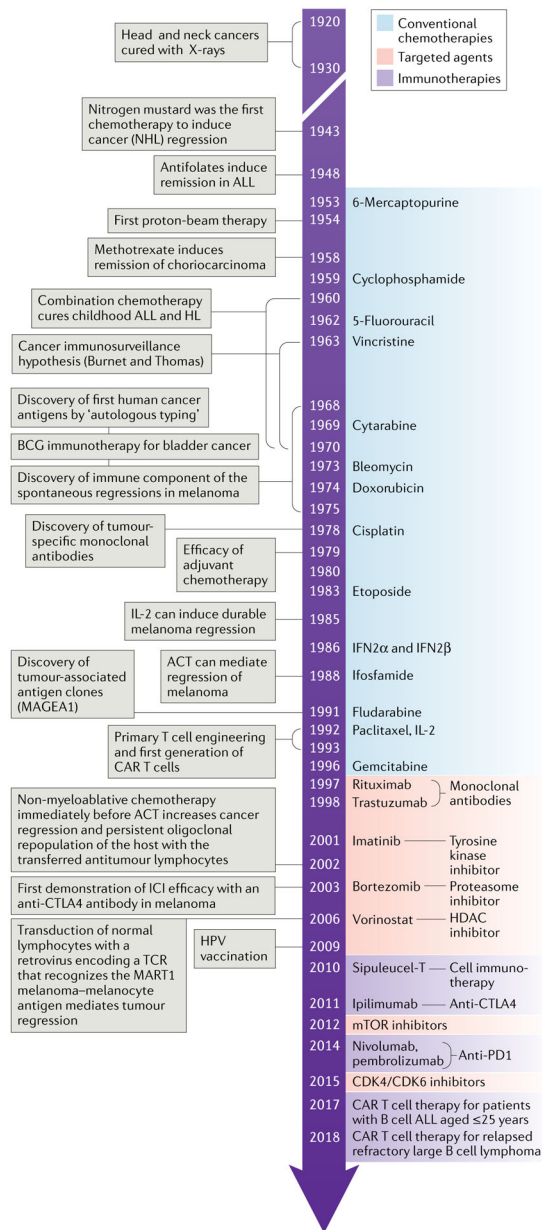


Fig. 2 |. Timeline of cancer therapy development.

The timeline presents landmarks in the development of cancer therapeutics. Three main eras can be distinguished on the basis of the type of agent: classic chemical compounds (shown in blue), targeted therapies (shown in pink) and immunotherapies (shown in purple). ACT, adoptive T cell therapy; ALL, acute lymphoblastic leukaemia; BCG, bacillus Calmette–Guérin; CAR, chimeric antigen receptor; CDK, cyclin-dependent kinase; CTLA4, cytotoxic T lymphocyte antigen 4; HDAC, histone deacetylase; HL, Hodgkin lymphoma; HPV, human papillomavirus; ICI, immune checkpoint inhibitor; MART1, melanoma antigen recognized by T cells 1; mTOR, mechanistic target of rapamycin; NHL, non-Hodgkin lymphoma; PD1, programmed cell death 1; TCR, T cell receptor.

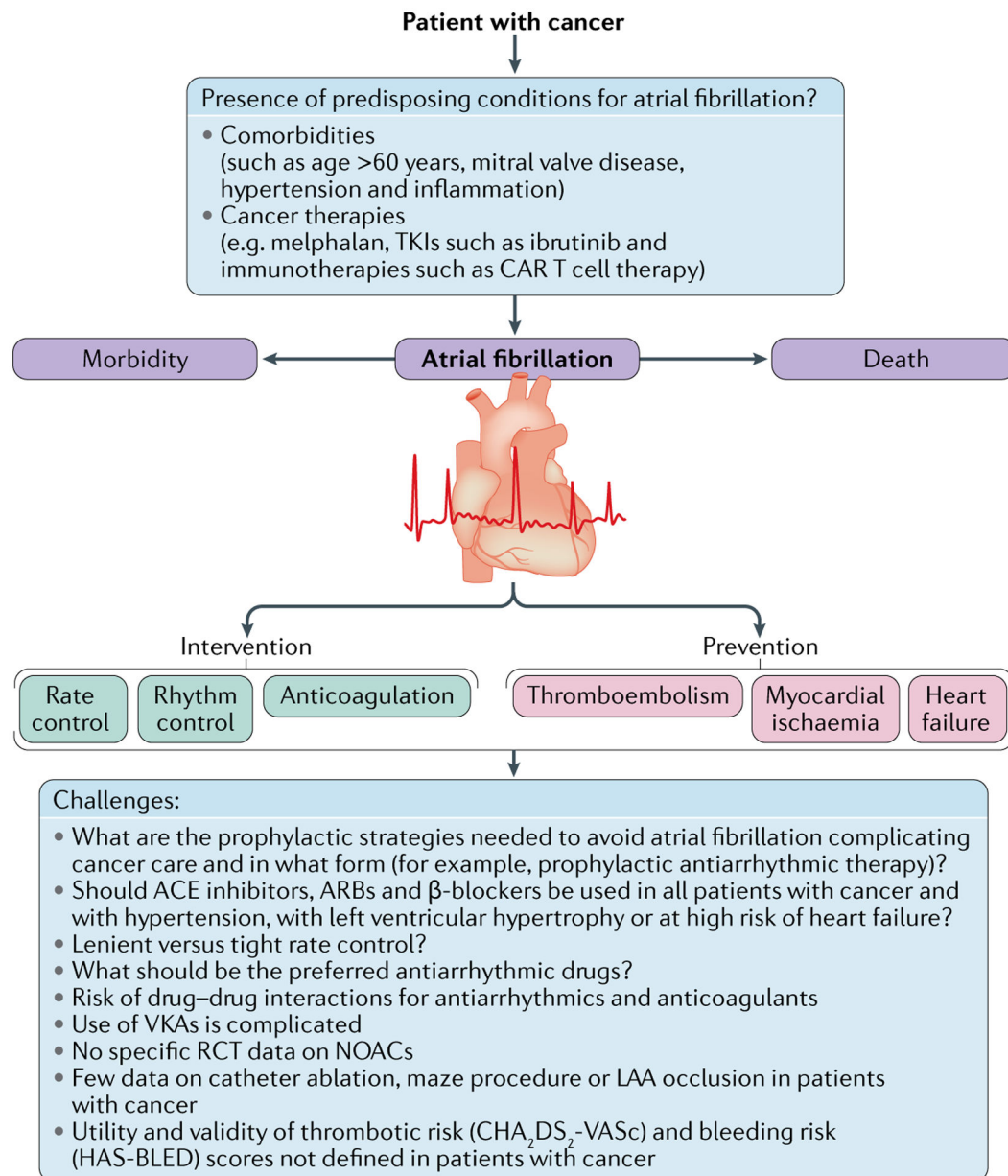


Fig. 3 |. Main elements in the treatment of patients with cancer and atrial fibrillation.

In patients with cancer, predisposing conditions for atrial fibrillation should be identified and addressed if possible. These include common risk factors for atrial fibrillation such as old age (>60 years), valvular heart disease, hypertension, obstructive sleep apnoea, chronic kidney disease, diabetes mellitus and smoking. Cancer therapies that have been associated with the risk of atrial fibrillation are listed in TABLE 4 and include chemical compounds such as melphalan, targeted agents such as the tyrosine kinase inhibitor (TKI) ibrutinib and immunotherapies that increase inflammation and cytokine production such as immune checkpoint inhibitor and chimeric antigen receptor (CAR) T cell therapies. Various other factors are important in patients with cancer, including metabolic (such as hyperthyroidism) and electrolyte abnormalities, autonomic nervous system stimulation (pain

or stress), cardiac infiltration or pericarditis and/or pericardial effusion. These predisposing factors can contribute to morbidity and death in patients with cancer. Atrial fibrillation symptoms include palpitations, chest discomfort and dyspnoea. Atrial fibrillation can lead to thromboembolism, myocardial ischaemia and heart failure. To reduce symptoms and the risk of complications, the decisions have to be made whether interventions should be pursued and what they should be. However, risk scores to guide decisions regarding anticoagulation have not been validated for patients with cancer. Similarly, results from landmark randomized clinical trials (RCTs) involving patients with atrial fibrillation cannot be easily translated to patients with cancer. ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; LAA, left atrial appendage; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.

Table 1 | Leading cardiovascular toxic effects of conventional chemotherapies and radiation therapy

Therapy	Cancer therapy indications (label and off-label)	Toxicity			
		Cardiac	Arrhythmia	Vascular	Other
Anthracyclines					
Doxorubicin	ALL, bladder cancer, breast cancer, endometrial carcinoma, Ewing sarcoma, hepatocellular cancer, HL, leukaemia or lymphoma, metastatic solid tumours, multiple myeloma, NHL, osteosarcoma, SCLC, soft-tissue sarcoma, thymoma, uterine sarcoma, Waldenström macroglobulinaemia	+++	+++	-	US black box warning: cardiomyopathy, secondary malignancy, extravasation and tissue necrosis, myelosuppression
Epirubicin	Breast cancer, gastric cancer, oesophageal cancer, osteosarcoma, soft-tissue sarcoma	+++	+++	-	
Idarubicin	AML	+++	-	-	
Mitoxantrone	AML, HL, NHL, prostate cancer, stem cell transplantation	++	+++	++	
Alkylating agents					
Busulfan	Essential thrombocythaemia, haematopoietic stem cell conditioning regimen, polycythaemia vera	-	+++	+++	Oedema, pericardial effusion, even tamponade US black box warning: bone marrow suppression
Cyclophosphamide	ALL, breast cancer, CLL, Ewing sarcoma, HL, multiple myeloma, NHL, SCLC, stem cell transplant conditioning	++	+	+	Bone marrow suppression
Ifosfamide	Bladder cancer, cervical cancer, Ewing sarcoma, HL, NHL, osteosarcoma, ovarian cancer, soft-tissue sarcoma, testicular cancer, thymoma	+	-	-	US black box warning: myelotoxicity, CNS toxicity, nephrotoxicity, haemorrhagic cystitis
Melphalan	Amyloidosis, multiple myeloma, ovarian cancer, HL, stem cell transplant conditioning (lymphomas)	-	++	-	US black box warning: bone marrow suppression, hypersensitivity, secondary malignancy
Antimetabolites					
5-Fluorouracil	Anal carcinoma, bladder cancer, breast cancer, cervical cancer, colorectal cancer, oesophageal cancer, gastric cancer, hepatobiliary cancer, pancreatic cancer, squamous cell carcinomas	++	++	+++	Bone marrow suppression
Capecitabine	Anal carcinoma, breast cancer, colorectal cancer, gastric cancer, hepatobiliary cancer, oesophageal cancer, ovarian, fallopian peritoneal cancer, pancreatic cancer, cancer of unknown primary	+	++	++	Bone marrow suppression, oedema US black box warning: warfarin interaction
Clofarabine	ALL, AML	+ (high dose or in combination with cyclophosphamide)	+++	-	Bone marrow suppression, pericardial effusion, capillary leak syndrome, hypotension, hypertension

Therapy	Cancer therapy indications (label and off-label)	Toxicity			
		Cardiac	Arrhythmia	Vascular	Other
Cytarabine	ALL, AML, acute promyelocytic leukaemia, CLL, CNS lymphoma, HL, meningeal leukaemia, NHL	Not defined	-	-	Bone marrow suppression, pericarditis
Gemcitabine	Adenocarcinoma of unknown primary, breast cancer, bladder cancer, cervical cancer, head and neck cancer, hepatobiliary cancer, HL, malignant pleural mesothelioma, NHL, NSCLC, ovarian cancer, pancreatic cancer, sarcomas, SCLC, testicular cancer, uterine cancer	-	-	+	Bone marrow suppression, oedema
Microtubule-binding agents					
Paclitaxel	Adenocarcinoma of unknown primary, bladder cancer, breast cancer, cervical cancer, head and neck cancers, Kaposi sarcoma, NSCLC, oesophageal and gastric cancer, ovarian cancer, penile cancer, SCLC, soft-tissue sarcoma, testicular germ cell tumours, thymoma	+	++	++	Oedema, hypotension, flushing US black box warning: hypersensitivity reaction and bone marrow suppression
Docetaxel	Adenocarcinoma of unknown primary, bladder cancer, breast cancer, Ewing sarcoma, head and neck cancers, NSCLC, oesophageal and gastric cancer, ovarian cancer, prostate cancer, SCLC, soft-tissue sarcoma	+	+	+	Neurotoxicity, bone marrow suppression, oedema, pericardial effusion, hypotension US black box warning: fluid retention, neutropenia, hypersensitivity, hepatic function impairment, increased mortality
Vinblastine	Bladder cancer, HL, melanoma, NSCLC, soft-tissue sarcoma, testicular cancer	-	-	+	Bone marrow suppression, pulmonary toxicity
Vincristine	ALL, CNS tumours, HL, NHL, Ewing sarcoma, gestational trophoblastic tumours, multiple myeloma, ovarian cancer, primary CNS lymphoma, SCLC, thymoma	-	-	+	Oedema, hypotension
Platinum-based drugs					
Cisplatin	Bladder cancer, breast cancer, cervical cancer, endometrial carcinoma, oesophageal and gastric cancer, head and neck cancer, HL, malignant pleural mesothelioma, multiple myeloma, NHL, osteosarcoma, ovarian cancer, penile cancer, SCLC, testicular cancer	+	+	++	US black box warning: myelosuppression, nephrotoxicity, peripheral neuropathy
Oxaliplatin	Biliary adenocarcinoma, CLL, cancer of unknown primary, colorectal cancer, neuroendocrine tumours (carcinoid), NHL, ovarian cancer, oesophageal/gastric cancers, pancreatic cancer, testicular cancer	-	+	++	Bone marrow suppression, oedema, peripheral neuropathy and neurotoxicity US black box warning: hypersensitivity and anaphylactic reactions
Antitumour antibiotics					
Bleomycin	HL, testicular cancer, ovarian germ cell cancer	-	-	+	Phlebitis US black box warning: pulmonary toxicity, idiosyncratic reaction
Immunomodulatory drugs					
Lenalidomide	CLL, diffuse large B cell lymphoma, mantle cell lymphoma, multiple myeloma, myelodysplastic syndrome	+	++	++	Oedema

Therapy	Cancer therapy indications (label and off-label)	Toxicity			
		Cardiac	Arrhythmia	Vascular	Other
Thalidomide	Multiple myeloma, systemic light chain amyloidosis, Waldenström macroglobulinaemia	-	+	+++	US black box warning: fetal risk, haemotoxicity, arterial and venous thromboembolic events Oedema US black box warning: risk in pregnancy and risk of fetal malformation, thromboembolic events
Radiation therapy					
Mainly external beam	Breast cancer, gastric cancer, head and neck cancer, lung cancer, lymphoma, oesophageal cancer, prostate cancer, testicular cancer	++	+	++	Valvular heart disease, pericarditis with/without constriction, restrictive cardiomyopathy

Based on data from Micromedex (IBM, NY, USA) and Lexicomp (Wolters Kluwer, Netherlands). Frequency of cardiovascular toxic effects: -, not reported; +, uncommon (<1%); ++, common (1–10%); +++, very common (>10%). ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; CNS, central nervous system; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer.

Table 2 |

Leading cardiovascular toxic effects of targeted cancer therapies

Therapy	Cancer therapy indications (label and off-label)	Toxicity			
		Cardiac	Arrhythmia	Vascular	Other
Proteasome inhibitors					
Bortezomib	Follicular lymphoma, mantle cell lymphoma, multiple myeloma, systemic light chain amyloidosis, T cell lymphoma, Waldenstrom macroglobulinaemia	++	+	+	Bone marrow suppression, hypotension
Carfilzomib	Multiple myeloma, Waldenstrom macroglobulinaemia	++	-	+++	Bone marrow suppression, oedema, pulmonary hypertension
HDAC inhibitors					
Panobinostat	Multiple myeloma	-	+++	++	Bone marrow suppression, peripheral oedema, orthostatic hypotension US black box warning: severe and fatal cardiac ischaemic events, severe arrhythmias and ECG changes, severe diarrhoea
Romidepsin	T cell lymphoma	-	++	++	Bone marrow suppression, oedema, hypotension
Vorinostat	T cell lymphoma	-	++	++	Bone marrow suppression, peripheral oedema
CDK4/CDK6 inhibitors					
Abemaciclib	Breast cancer	-	-	+	-
Ribociclib	Breast cancer	-	++	-	Peripheral oedema, syncope
mTOR inhibitors					
Everolimus	Breast cancer, neuroendocrine tumours, RCC	++	++	++	Bone marrow suppression, peripheral oedema, hypertension
Temsirolimus	RCC	-	-	+++	Bone marrow suppression, peripheral oedema, hypertension
Monoclonal antibodies (target)					
Alemtuzumab (anti-CD52)	B cell CLL, aplastic anaemia, T cell lymphocytic and prolymphocytic leukaemia	+	++	++	Peripheral oedema, hypotension, hypertension US black box warning: autoimmunity, infusion reactions, and malignancies, myelosuppression, infection, stroke
Rituximab (anti-CD20)	Burkitt lymphoma, CLL, CNS lymphoma, HL, NHL, Waldenstrom macroglobulinaemia	+	+	++	Peripheral oedema, hypertension, hypotension, flushing US black box warning: infusion reactions, mucocutaneous reactions, progressive multifocal leukoencephalopathy
Cetuximab (anti-EGFR/HER1)	Colorectal cancer, head and neck cancer, penile cancer, squamous cell skin cancer (KRAS wild type)	-	+	++	US black box warning: cardiopulmonary arrest, infusion reactions
Necitumumab (anti-EGFR/HER1)	NSCLC	-	-	+++	US black box warning: cardiopulmonary arrest, hypomagnesaemia

Therapy	Cancer therapy indications (label and off-label)	Toxicity			
		Cardiac	Arrhythmia	Vascular	Other
Panitumumab (anti-EGFR/HER1)	Colorectal cancer, <i>KRAS</i> wild type	-	-	+	US black box warning: dermatological toxicity
Pertuzumab (anti-HER2/ERBB2)	Breast cancer	++	-	-	Peripheral oedema US black box warning: cardiotoxicity, birth defects
Trastuzumab (anti-HER2/ERBB2)	Breast cancer, gastric cancer	+++	++	-	Peripheral oedema US black box warning: cardiotoxicity, pulmonary toxicity, infusion reactions, birth defects
Aflibercept (anti-VEGF-VEGFR2)	Metastatic colorectal cancer	+	-	++	Hypertension, reversible posterior leukoencephalopathy syndrome, thrombotic microangiopathy US black box warning: haemorrhage, GI tract perforation, compromised wound healing
Bevacizumab (anti-VEGF-VEGFR2)	Glioblastoma, persistent/recurrent/metastatic cervical cancer, metastatic colorectal cancer, (non-squamous) NSCLC, ovarian (epithelial), fallopian tube or primary peritoneal cancer, metastatic RCC	++	-	+++	Oedema, hypotension, hypertension, reversible posterior leukoencephalopathy syndrome, thrombotic microangiopathy US black box warning: haemorrhage, GI tract perforation, compromised wound healing
Ramucicumab (anti-VEGF-VEGFR2)	Metastatic NSCLC, metastatic gastric cancer, metastatic colorectal cancer	-	-	++	Hypertension, reversible posterior leukoencephalopathy syndrome, thrombotic microangiopathy
Multi-target kinase inhibitors (primary target)					
Erlotinib (EGFR/HER1)	NSCLC, pancreatic cancer	-	++	+++	Oedema, pulmonary toxicity
Osimertinib (EGFR/HER1)	NSCLC	++	++	-	Bone marrow suppression, pulmonary toxicity
Dacomitinib (EGFR/HER1)	NSCLC	-	-	++	Pulmonary toxicity
Lapatinib (HER2/ERBB2)	Breast cancer	++	+	-	Pulmonary toxicity US black box warning: hepatotoxicity
Axitinib (VEGFR1-VEGFR3)	RCC, thyroid cancer	+	-	++	Hypertension, haemorrhage
Lenvatinib (VEGFR1-VEGFR3)	Hepatocellular cancer, RCC, thyroid cancer	++	++	++	Peripheral oedema, hypertension
Pazopanib (VEGFR1-VEGFR3)	RCC, soft-tissue carcinoma, thyroid cancer	+++	+++	++	Peripheral oedema, hypertension, thrombotic microangiopathy, bleeding, pulmonary toxicity US black box warning: hepatotoxicity
Sorafenib (VEGFR1-VEGFR3)	Angiosarcoma, hepatocellular cancer, RCC, thyroid cancer, GIST	++	+	++	Hypertension, bleeding
Sunitinib (VEGFR1-VEGFR3)	GIST, pancreatic neuroendocrine tumours, RCC, soft-tissue sarcoma, thyroid cancer	+++	+	+++	Hypertension, thrombotic microangiopathy, increased creatine kinase level US black box warning: hepatotoxicity

Therapy	Cancer therapy indications (label and off-label)	Toxicity			
		Cardiac	Arrhythmia	Vascular	Other
Vandetanib (VEGFR)	Thyroid cancer	++	+++	++	Hypertensive crisis, bleeding, pulmonary toxicity US black box warning: QT interval prolongation, torsades de pointes, sudden cardiac death
Regorafenib (VEGFR2)	Colorectal cancer, GIST, hepatocellular carcinoma	-	-	++	Hypertension US black box warning: hepatotoxicity
Bosutinib (BCR-ABL)	Philadelphia chromosome-positive CML	-	++	++	Oedema, chest pain, pericardial effusion, hypertension
Dasatinib (BCR-ABL1)	Philadelphia chromosome-positive ALL and CML, GIST	-	++	++	Oedema, pulmonary hypertension
Imatinib (BCR-ABL1)	Philadelphia chromosome-positive ALL and CML, GIST, myelodysplastic syndrome, melanoma, stem cell transplant for CML	+	++	++	Palpitations, oedema, chest pain, subdural haematoma
Nilotinib (BCR-ABL1)	Philadelphia chromosome-positive ALL and CML, GIST	-	++	+++	Oedema, hyperglycaemia, hypercholesterolaemia US black box warning: QT interval prolongation, sudden cardiac death
Ponatinib (BCR-ABL1)	Philadelphia chromosome-positive ALL and CML	++	+++	+++	Bone marrow suppression, bleeding, hypertensive crisis, thrombotic microangiopathy US black box warning: hepatotoxicity, arterial occlusion, venous thromboembolism
Ibrutinib (BTK)	CLL, mantle cell lymphoma, marginal zone lymphoma, Waldenstrom macroglobulinaemia	-	+++	-	Oedema, hypertension, subdural haematoma
Alectinib (ALK)	NSCLC	-	+++	++	Oedema, pulmonary toxicity
Brigatinib (ALK)	NSCLC	-	++	-	Hypertension, pulmonary toxicity
Ceritinib (ALK)	NSCLC	-	+++	-	Pericarditis, pericardial effusion, pulmonary toxicity
Crizotinib (ALK)	NSCLC	-	+++	++	Oedema, pulmonary toxicity
Lorlatinib (ALK)	NSCLC	-	++	-	Oedema, pulmonary toxicity
Dabrafenib (BRAF)	Melanoma, NSCLC, thyroid cancer	++	-	-	Bleeding, oedema, hypertension
Encorafenib (BRAF)	Melanoma	-	+	-	Facial paresis
Vemurafenib (BRAF)	Melanoma, NSCLC	-	+++	-	Oedema, nephrotoxicity, hypertension
Gilteritinib (FLT3)	Relapsed or refractory FLT3+AML	++	++	-	Oedema, hypotension, hypertension, pericardial effusion, pericarditis
Ruxolitinib (JAK)	Myelofibrosis, polycythaemia vera	-	+	-	Oedema
Cabozantinib (MET)	Hepatocellular carcinoma, RCC, thyroid cancer	-	++	++	Bone marrow suppression, hypertension
Binimetinib (MEK)	Melanoma	++	-	++	Oedema, bleeding, pulmonary toxicity, hypertension

Therapy	Cancer therapy indications (label and off-label)	Toxicity			
		Cardiac	Arrhythmia	Vascular	Other
Cobimetinib (MEK)	Melanoma	+++	-	-	Bleeding, hypertension
Trametinib (MEK)	Melanoma, NSCLC, thyroid cancer	+++	++	-	Oedema, bleeding, pulmonary toxicity, hypertension

Based on data from Micromedex (IBM, NY, USA) and Lexicomp (Wolters Kluwer, Netherlands). Frequency of cardiovascular toxic effects: -, not reported; +, uncommon (<1%); ++, common (1–10%); +++, very common (>10%). ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CDK, cyclin-dependent kinase; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; CNS, central nervous system; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; GI, gastrointestinal; GIST, gastrointestinal stromal tumour; HDAC, histone deacetylase; HL, Hodgkin lymphoma; JAK, Janus kinase; MEK, MAPK/ERK kinase; NHL, non-Hodgkin lymphoma; NSCLC, non-small-cell lung cancer; mTOR, mechanistic target of rapamycin; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Table 3 |

Leading cardiovascular toxic effects of cancer immunotherapies

Therapy (target)	Cancer therapy indications (label and off-label)	Toxicity			
		Cardiac	Arrhythmia	Vascular toxicity	Other
Immune checkpoint inhibitors					
Ipilimumab (anti-CTLA4)	Colorectal cancer, melanoma, RCC, SCLC	+	+	+	US black box warning: immune-mediated adverse reactions
Nivolumab (anti-PD1)	Colorectal cancer, HNSCC, hepatocellular carcinoma, HL, melanoma, NSCLC, RCC, SCLC, urothelial carcinoma	+	+	++	Immune-mediated adverse events, peripheral oedema, hypertension
Pembrolizumab (anti-PD1)	Cervical cancer, gastric cancer, HNSCC, hepatocellular carcinoma, HL, melanoma, Merkel cell carcinoma, NSCLC, primary mediastinal large B cell lymphoma, urothelial carcinoma	+	+	+	Immune-mediated adverse events, oedema, pericarditis, pericardial effusion
Atezolizumab (anti-PDL1)	Breast cancer (triple negative), NSCLC, SCLC, urothelial carcinoma	+	-	+	Immune-mediated adverse events, peripheral oedema
Avelumab (anti-PDL1)	Merkel cell carcinoma, urothelial carcinoma	+	-	-	Immune-mediated adverse events, peripheral oedema, hypertension
Durvalumab (anti-PDL1)	Non-small-cell carcinoma, urothelial carcinoma	+	-	-	Immune-mediated adverse events, peripheral oedema
CAR T cell therapy					
Tisagenlecleucel (anti-CD19)	ALL, diffuse large B cell lymphoma	++	+++	++	Hypotension, hypertension US black box warning: cytokine release syndrome, neurotoxicity

Based on data from Micromedex (IBM, NY, USA) and Lexicomp (Wolters Kluwer, Netherlands). Frequency of cardiovascular toxic effects: -, not reported; +, uncommon (<1%); ++, common (1-10%); +++, very common (>10%). ALL, acute lymphoblastic leukaemia; CAR, chimeric antigen receptor; CTLA4, cytotoxic T lymphocyte antigen 4; HL, Hodgkin lymphoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small-cell lung cancer; PD1, programmed cell death 1; PDL1, programmed cell death 1 ligand 1; RCC, renal cell carcinoma; SCLC, small-cell lung cancer.

Table 4 |

Types of arrhythmia reported with the use of cancer therapies

Therapy class	Agent (target)	AF	SVT	Bradycardia	AV block	QTc prolongation	TdP	VT/VF	SCD
Miscellaneous	Arsenic trioxide	++	++	-	+	+++	++	+	+
Alkylating agents	Anthracyclines; acute	ND	ND	ND	ND	ND	-	ND	ND
	Busulfan	ND	ND	-	ND	-	-	-	ND
	Cyclophosphamide	ND	ND	-	ND	ND	-	ND	-
	Ifosfamide	ND	-	ND	-	-	-	ND	ND
	Melphalan	ND	ND	-	-	-	-	ND	ND
Antimetabolites	5-Fluorouracil	ND	ND	ND	ND	ND	-	ND	ND
	Capecitabine	++	-	++	-	+	-	-	+
	Clofarabine	ND	ND	ND	-	-	-	-	-
	Cytarabine	ND	-	ND	-	-	-	-	-
	Gemcitabine	+	+	-	-	-	-	-	-
Microtubule-binding agents	Paclitaxel	+	+	++	+	-	-	+	-
	Cisplatin	+	+	+	+	-	-	+	-
Immunomodulatory drugs	Lenalidomide	ND	ND	ND	-	-	-	-	-
	Thalidomide	+	+	+	-	-	-	-	-
Proteasome inhibitors	Bortezomib	ND	-	ND	ND	ND	ND	ND	ND
	Carfilzomib	ND	ND	ND	ND	-	-	-	ND
HDAC inhibitors	Romidepsin	+	++	-	-	++	+	++	+
	Panobinostat	-	-	-	-	++	-	-	-
	Vorinostat	-	-	ND	-	++	-	-	-
CDK4/CDK6 inhibitors	Ribociclib	-	-	-	-	++	-	-	-
	Everolimus	++	-	-	-	-	-	-	-
Monoclonal antibodies	Alemtuzumab (anti-CD52)	++	-	++	-	-	-	+	+
	Cetuximab (anti-EGFR/HER1)	+	-	+	-	-	-	+	+
	Necitumumab (anti-EGFR/HER1)	-	+	-	-	-	-	-	++
	Pertuzumab (anti-EGFR/HER1)	+	+	+	-	-	-	-	+
	Rituximab (anti-CD20)	+	+	+	+	+	+	+	+

Therapy class	Agent (target)	AF	SVT	Bradycardia	AV block	QTc prolongation	TdP	VT/VF	SCD
Multi-target kinase inhibitors	Trastuzumab (anti-HER2/ERBB2)	++	++	+	-	-	-	+	-
	Osimertinib (EGFR/HER1)	-	-	-	-	++	-	-	-
	Lapatinib (HER2/ERBB2)	+	+	-	-	+	-	-	-
	Lenvatinib (VEGFR)	-	-	-	-	++	-	-	-
	Pazopanib (VEGFR)	-	-	+++	-	++	-	-	-
	Sorafenib (VEGFR)	+	-	+	+	+	+	-	-
	Sunitinib (VEGFR)	-	-	+	-	+	+	-	-
	Vandetanib (VEGFR)	-	-	-	-	+++	-	+	+
	Bosutinib (BCR-ABL1)	-	-	+	-	++	-	-	-
	Dasatinib (BCR-ABL1)	+	+	-	-	+	-	+	+
	Imatinib (BCR-ABL1)	+	+	-	-	-	-	-	-
	Nilotinib (BCR-ABL1)	++	-	++	++	++	-	-	+
	Ponatinib (BCR-ABL1)	++	+	+	+	+	-	+	-
	Ibrutinib (BTK)	+++	-	-	-	-	-	-	+
	Alectinib (ALK)	-	-	+++	-	+	-	-	-
	Ceritinib (ALK)	-	-	+	-	-	-	-	-
	Crizotinib (ALK)	-	-	+++	-	+	-	-	-
Brigatinib (ALK)	-	-	++	-	-	-	-	-	
Lorlatinib (ALK)	-	-	-	+	-	-	-	-	
Immune checkpoint inhibitors	Encorafenib (BRAF)	-	-	-	-	+	-	-	-
	Vemurafenib (BRAF)	++	+	+	-	+++	+	-	-
	Gilteritinib (FTL3)	-	-	-	-	++	-	-	-
	Trametinib (MEK)	-	-	++	-	++	-	-	-
	Ruxolitinib (JAK)	-	-	+	-	+	-	-	-
	Ipilimumab (anti-CTLA4)	+	-	+	+	-	-	+	+
	Nivolumab (anti-PD1)	+	-	+	+	-	-	+	+
CAR T cell therapy	Pembrolizumab (anti-PD1)	+	-	+	+	-	-	+	+
	Tisagenlecleucel (anti-CD19)	++	++	-	-	-	-	-	-

Frequency not always defined for the individual entities, but when available: -, not reported or very few data available; +, uncommon (<1%); ++, common (1-10%); +++, very common (>10%). AF, atrial fibrillation; AV, atrioventricular; CAR, chimeric antigen receptor; CDK, cyclin-dependent kinase; CTLA4, cytotoxic T lymphocyte antigen 4; EGFR, epidermal growth factor receptor; HDAC, histone

deacetylase; JAK, Janus kinase; MEK, MAPK/ERK kinase; mTOR, mechanistic target of rapamycin; ND, frequency not defined; PD1, programmed cell death 1; QTc, corrected QT interval; SCD, sudden cardiac death; SVT, supraventricular tachycardia; TdP, torsades de pointes; VEGFR, vascular endothelial growth factor receptor; VF, ventricular fibrillation; VT, ventricular tachycardia.

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