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Cardio-oncology - strategies for management of cancer-therapy related cardiovascular disease

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ABSTRACT

Current therapy of advanced cancers is based on several modalities including radiotherapy, cytotoxic chemotherapy, molecularly targeted inhibitors and antibodies targeting immune checkpoints. All of those these modalities can negatively impact the cardiovascular system, and there is considerable experience in relation to radiotherapy and chemotherapy. In contrast, the knowledge base on cardiovascular toxicities of novel agents targeting signal transduction pathways and immune regulation is quite limited. In particular, potential late effects are of concern as cardiovascular pathology can negatively impact quality of life and prognosis in cancer survivors, particularly when additional cardiovascular risk factors are present. Treatment-associated adverse events include hypertension, venous thromboembolism, coronary artery disease, valvular heart disease, heart failure and arrhythmias. Early diagnosis of subclinical cardiotoxic effects of cancer therapies remains challenging. Integrated care, as provided by multidisciplinary cardio-oncology teams is the best option for prevention, diagnosis and treatment of cardiovascular diseases associated with cancer therapy. This review considers the cardiotoxic effects of specific cancer therapies and discusses novel diagnostic and therapeutic approaches as a reference for optimizing the care of cancer patients receiving novel cancer therapies.

1. Introduction

Modern treatment strategies have improved short- and long-term relapse-free survival in cancer patients [1]. Many patients with childhood- or adult-onset cancer are cured or live for ten years or longer [2]. Consequently, increasing numbers of adverse cardiovascular events in cancer survivors indicate that success in cancer care comes at a price [3].

Early stage cancers are surgically treated. Patients with advanced or metastatic cancers often require multiple modalities, including radiotherapy, cytotoxic chemotherapy, molecularly targeted inhibitors and antibodies targeting signal transduction pathways and immune checkpoints. The more advanced the cancer, the more potentially cardiotoxic therapy is used. These treatments also impact the cardiovascular system, and such impact may become clinically evident even years after completion of therapy [4,5]. Quality of life in cancer survivors may be limited by cardiotoxic complications, and many patients die not from cancer recurrence, but from cardiovascular disease. Treatment-related cardiovascular events have been covered and reported in cancer trials. However, the spectrum of cardiotoxicity for the large number of novel cancer medicines that have been introduced in the past decade is not well defined, and this is particularly true for long-term sequelae [6]. The growing concern over cancer therapy-associated cardiotoxicity has opened the new field of cardio-oncology. A multidisciplinary approach involving cardiologists, oncologists, radiologists and nuclear medicine physicians will provide individualized risk assessment, prevention and early detection of toxicities and optimized care.

Cardio-oncology aims to provide comprehensive care for cancer patients with or at risk for cardiovascular disease. Today, definitions of cardiotoxicity related to cancer therapy and its epidemiology remain incomplete [4,7], guidelines are pending, and there is little evidence from randomized, controlled clinical trials [3]. Uncertainty exists as to which patients should be referred to a cardio-oncology unit for screening and specific disease-related treatments. Treatment recommendations are mainly based on established guidelines for cardiovascular diseases that were not tailored to the need of cancer patients, or from consensus recommendations in oncology practice guidelines.

In the present review, we outline cardiotoxic effects of clinically relevant classes of cancer therapies. We further propose criteria for

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selection of patients to be referred to a cardiologist or cardio-oncology unit. We discuss strategies for the diagnosis of treatment-related adverse cardiovascular effects in cancer patients. We consider limitations of current prevention and treatment regimens for treatment-related cardiovascular disease and highlight the need for specific trials in cancer patients. Finally, we propose rational algorithms for the prevention and treatment of adverse cardiovascular effects, particularly with novel cancer therapies.

2. Assessment before cancer therapy – preexisting risk factors and cardiovascular disease

Globally, cardiovascular and malignant disease are the most common causes of death with >65% of deaths attributed to either condition in developed countries. However, there is little awareness that these two pathologies are connected at multiple levels. Both heart disease and cancer share several common risk factors (hypertension, dyslipidemia, diabetes mellitus, obesity, smoking, age and sex), and risk reduction strategies result in positive outcomes for both diseases. Good cardiovascular health also supports cancer therapy and reduces adverse cancer therapy-related cardiovascular events, while preexisting cardiovascular risk factors come with increased cardiotoxicities [8–13]. Finally, clinically evident cardiovascular disease may require a preliminary diagnostic work-up or even preclude patients from specific cancer treatments [8]. Cardiovascular risk factors predispose to cardiotoxicity from cancer therapy, particularly from therapies associated with left ventricular dysfunction and heart failure (e.g. anthracyclines). The risk to develop signs of cardiotoxicity is increased in older patients (>60 years) and further increased in the presence of at least two of the following risk factors: hypertension, dyslipidemia, diabetes mellitus, obesity, smoking [8–13]. The individual risk profile must be particularly considered for patients scheduled for 'high risk' cancer therapies (Supplementary Table 1, e.g. anthracycline therapy). Not every patient will benefit from a strict regulation of these risk factors before, during and after therapy. Cardio-oncology is probably less relevant for patients with poor prognosis or frailty. On the other hand, large numbers of e.g. younger breast cancer patients will likely profit from risk factor monitoring. All risks should therefore be managed according to current AHA/ESC guidelines in patients with good prognosis [3,8,14,15].

Cardiovascular disease (particularly previous myocardial infarction and valvular disease) greatly increases the risk for toxicities, particularly in patients receiving anthracycline-based chemotherapies [16–18]. The relation of risk factors to side effects from the novel therapies (molecularly targeted inhibitors or immune therapies released over the past years) is of growing concern [19]. Whenever feasible, a detailed assessment of the patient's history prior to administration of cardiotoxic agents is recommended. This consideration should be directed at any signs of angina, exertional dyspnea, syncope, palpitations, claudication and edema. An electrocardiogram (ECG) is mandatory in patients receiving chemotherapy (e.g. for concurrent arrhythmias and/or as baseline reference in case of cardiovascular events under therapy). The benefit from assessment of biomarkers before chemotherapy is unclear. In an unselected cohort, elevated troponin levels prior to administration of a cardiotoxic drug predicted mortality during follow-up [20]. Biomarkers are recommended by current AHA/ESC guidelines for the detection of significant cardiovascular pathologies. Overt cardiovascular disease is treated according to current guidelines. However, the need for rapid initiation of cancer therapy in symptomatic patients or patients with high tumor load may require individual decisions, including the treatment of three-vessel coronary artery disease, aortic stenosis or mitral valve regurgitation by catheter-based approaches rather than surgery in younger patients. Such approach avoids delay from surgery and subsequent recovery before cancer therapy. Another important issue is to minimize the use of cardiovascular interventions and devices requiring highly intensive and prolonged anticoagulation/anti-platelet medication, which can greatly increase the risk of hematotoxic cancer therapies and/or interventions (e.g. mechanical heart valves). Multidisciplinary discussion between the treating oncologist and cardiologist and with the surgery team is mandatory.

3. Cardiotoxicity of selected/clinically relevant cancer therapies

The cardiotoxicity of cytotoxic agents e.g. anthracyclines or high doses of alkylating agents, and radiation fields involving thorax, brain and critical vascular structures has long been appreciated [3,14,15]. However, the adverse effects of novel treatments, such as protein kinase inhibitors and immune checkpoint inhibitors (ICI, Supplementary Table 1), and algorithms for their optimal management remain an area of study.

3.1. Radiotherapy

With the favorable development of long-term survival in certain cancers the toxic effects of chest irradiation have become appreciated. The relative contribution of radiation vs. chemotherapy can often only be estimated. Radiotherapy is used in about 35% of cancer patients within one year of diagnosis, provided that there is an adequate infrastructure [21]. Pericarditis can occur early after high dose radiotherapy and has long been the only quantitatively considered radiotoxicity to the heart, with a risk of 5% at 5 years after doses of 40 Gy to the whole organ with conventional fractionation [22]. Pericarditis may present in its effusive or constrictive form, and the latter is difficult to diagnose [23]. Acute pericarditis has become rare due to advances in radiation techniques and is characterized by massive immune infiltration and exudation. Chronic pericarditis, however, is one of the most frequent radiation-induced cardiotoxicities and also occurs following low-dose radiation [24]. Twenty percent of patients with chronic pericarditis develop clinical signs of constriction. The diagnostic workup includes echocardiography and invasive hemodynamics [25], and complete surgical pericardiectomy remains the definite therapy. Radiation dose limits for pericarditis were employed in contemporary trials on definitive radio-chemotherapy for lung cancer [26]. With the advent of 3D conformal treatment planning in radiotherapy, dose distributions within the heart are calculated before radiotherapy [27]. Meanwhile, long-term follow-up of larger cohorts of patients with tumors of good prognosis, particularly breast cancer and Hodgkin's lymphoma, are available. Dose-dependent adverse effects of radiotherapy on the heart manifest as ischemic heart disease [28], valvular heart disease, cardiomyopathy and congestive heart failure [29].

Ischemic heart disease is the most common adverse cardiovascular event after radiotherapy for breast cancer [28]. Ionizing radiation exposure of the heart increases the individual patient's base line risk of ischemic heart disease by 7.4% per Gy mean heart dose, and this excess relative risk remains rather constant during follow-up until 20 years after radiotherapy. Comorbid patients with preexisting cardiac risk factors have a larger absolute excess risk of ischemic heart disease than patients without risk factors after the same radiation exposure. The 'Early Breast Cancer Trialists' Collaborative Group' analyzed the risk of heart disease in >40,000 women from 75 trials randomized to breast cancer radiotherapy vs. no radiotherapy [30] and found an increase in the relative risk of cardiac mortality of 4.1% per Gy mean heart dose [30]. The most common cause of radiation-dependent cardiac mortality in this analysis was ischemic heart disease followed by heart failure and valvular disease. Comparing toxicities in patients who receive tangential field radiotherapy for left-sided versus right-sided breast cancer, an increased risk of cardiac mortality was found in patients treated with left-sided radiotherapy [31].

Mediastinal radiotherapy for Hodgkin's lymphoma is usually given by opposing ap-pa fields. As a consequence, the dose distribution in the heart differs from that in breast cancer patients with a higher exposure of the atrio-ventricular annular plane. The excess relative risk of valvular heart disease increased by 2.5% per Gy for doses ≤ 30 Gy, and

disproportionally by 6.5% per Gy, 11.2% per Gy, and 24.3% per Gy for doses between >30–35.9 Gy, 36–40 Gy, and >40 Gy, respectively [32]. More than 70% of patients experienced higher-grade valvular heart disease with progression over time. The median time interval between diagnosis of Hodgkin's lymphoma and diagnosis of valvular heart disease was 23 years. Systematic cardiovascular screening of childhood cancer survivors after thoracic radiotherapy identified a high number of patients with valvular disease and heart failure not detected prior to screening [30]. The excess relative risk of coronary heart disease has a linear dose-response with a steepness of 7.4% per Gy mean heart dose, similar to breast cancer [33].

While the use of radiotherapy for childhood cancer is decreasing and total radiation doses and volumes are reduced in Hodgkin's lymphomas [34], other indications for thoracic radiotherapy such as stereotactic ablative radiotherapy for lung cancer and internal mammary node irradiation for breast cancer are considered more often. The prognosis of locally advanced lung cancer is improved after definitive radiochemotherapy, so that cardiovascular late effects become increasingly relevant especially in patients with cardiac risk factors. As the dose distribution in the heart can be estimated before radiotherapy, the individual risk of cardiovascular side effects can be predicted and the surveillance for toxicities tailored accordingly. Awareness of potential cardiovascular side effects led to optimizations of delivered dose distributions by better radiation techniques, such as treatment of lung tumors with intensity-modulated radiotherapy or of left-sided breast cancer in inspiratory breath-hold [35].

High dose radiotherapy increases intima-media thickness in large arteries such as the carotid artery [36]. Increases in carotid intima-media thickness can be detected within 90 days after radiotherapy by ultrasound and represent a risk factor for stroke [37]. Therefore, imaging and surveillance are recommended for early detection of severe stenosis and selection of patients who require treatment.

Endothelial cells are radiosensitive to apoptosis [38]. After brain radiotherapy at lower total doses down to 10 Gy with doses < 2 Gy per fraction, diffusion tensor magnetic resonance imaging revealed changes in white matter mean diffusivity and fractional anisotropy parameters related to vascular permeability. Changes increased over time and were detectable after 4–6 months at doses of 30–40 Gy. Diffusion changes in the parahippocampal cingula were found to be related to cognitive decline after radiotherapy [39]. Whole brain radiotherapy can impair cognitive function and does not improve survival when given in combination with stereotactic radiotherapy. Therefore, focal stereotactic radiotherapy alone is recommended for patients with one to three brain metastases [40].

3.2. Classical chemotherapy

Classical chemotherapy involves a variety of drugs and a broad spectrum of cardiotoxicity (Supplementary Table 1). Anthracyclines are prototypic cardiotoxic agents. Anthracyclines are used in childhood and adult cancers, and their cardiotoxic effects are dose-dependent (Fig. 1): Anthracyclines have multiple cellular and subcellular targets, which contribute to their cardiotoxicity.

A multiple stress theory has been forwarded, which particularly refers to the generation of toxic reactive oxygen species (ROS) and the inhibition of topoisomerase IIβ: Anthracyclines are enzymatically converted in a redox reaction (quinone to semiquinone), and this conversion results in the ROS at multiple cellular locations. Also, anthracyclines react with iron ions, e.g. from heme proteins, to generate ROS [41]. ROS oxidize and thus damage DNA, proteins and lipids [42]. Oxidation of contractile proteins contributes to cardiac contractile dysfunction [43]. ROS also stabilize p53, which consecutively initiates senescence and apoptotic cell death [44]. One of the major adverse events is the anthracycline-dependent interaction with topoisomerase IIβ, which is required for the repair of ROS-induced DNA damage. Impaired nuclear transcription reduces the synthesis of contractile elements and mitochondrial biogenesis (via reduced formation of PGC1α/β) [45]. Topoisomerase Iiβ knockout mice are protected from cardiotoxicity. In mitochondria, anthracyclines through increased ROS formation promote DNA damage and opening of the mitochondrial permeability transition pore, which, in turn, results in collapse of the mitochondrial membrane potential, disruption of the outer mitochondrial membrane, release of cytochrome C into the cytosol and the initiation of cell death [46]. Interference of anthracyclines with calcium channels increases intracellular calcium levels and induces calcium overload, which activates various proteases, e.g. calpains to induce cell death through autodigestion and impairs contractile function [47,48]. ROS and calcium act in concert to further promote permeabilization of the mitochondrial outer membrane [46]. In the vasculature, endothelial NO synthase (eNOS) activity is reduced, whereas cytosolic calcium is increased in smooth muscle cells [49], favoring the development of hypertension in anthracycline-treated patients and explaining the particular sensitivity of patients with endothelial dysfunction to the development of heart failure [50]. The multiple sites of anthracycline action are reflected in the enhanced susceptibility of specific patients with genetic variants [51]. Given these multiple events, it appears reasonable that anthracycline related cardiotoxicity may occur at early and very late stages during and after therapy. The multitude of deleterious actions also explains the potentially enhanced sensitivity to anthracyclines with pre-existing or intervening cardiovascular pathologies of other origin in the sense of a “multiple-stress hypothesis”.

In clinical practice, cumulative anthracycline doses are associated with the risk of developing heart failure. Accordingly, such cumulative doses are avoided whenever clinically possible. Possibly, peak drug levels and associated toxicity are reduced by prolonged infusion protocols, which are particularly used in pediatric oncology [52]. In preclinical experiments, ischemic conditioning protects cardiomyocytes from anthracycline-induced cells death [53], but this strategy remains to be addressed in further translational and clinical studies.

Doxorubicin, daunorubicin, epirubicin, idarubicin, and mitoxantrone induce heart failure [4]. Heart failure is an independent predictor of mortality in anthracycline recipients, and the majority of patients with established anthracycline-related heart failure die over the following two years. The outcome of established anthracycline-related heart failure is comparable to that of matched cohorts with dilative heart failure [14]. Primary prevention and treatment according to heart failure guidelines are, therefore, recommended. Heart failure goes along with arrhythmias, and vascular side effects can become manifest as hypertension and/or thrombosis [1,14,15].

Anthracyclines and HER2 inhibitors (e.g., the antibody trastuzumab or the small molecule inhibitor lapatinib) are standard of care in systemic treatment of patients with HER2-positive breast cancer in the adjuvant and in the palliative setting, and in palliative therapy of HER2-positive gastric cancer. As HER2 inhibitors per se have cardiotoxic potential [4], the simultaneous application of these agents with anthracyclines is avoided in particular in patients treated in a curative setting. The cellular signaling following combined anthracycline and HER2 inhibition is not fully clear; however, inhibition of the HER2 receptor on cardiomyocytes and the corresponding signal transduction promotes increased ROS formation [54]. Consequently, most treatment protocols sequence these agents with e.g. trastuzumab co-administered with taxanes. Also, anthracycline-free protocols have been developed, which are particularly appropriate in patients at high risk for cardiotoxicity.

Alkylating agents (e.g. cyclophosphamide and ifosfamide) have a broad spectrum of indications including lymphomas, leukemia, solid tumors and autoimmune disorders. The occurrence of cardiotoxicity is dose-dependent and may develop within 7 to 10 days after the initial administration in high dose regimens [55]. Cyclophosphamide induces vascular injury; lipid peroxidation and mitochondrial dysfunction have been related to ROS formation and DNA damage [56].

Fluoropyrimidines, such as 5-fluorouracil, are widely used in treatment of solid tumors. These drugs may induce acute chest pain as a

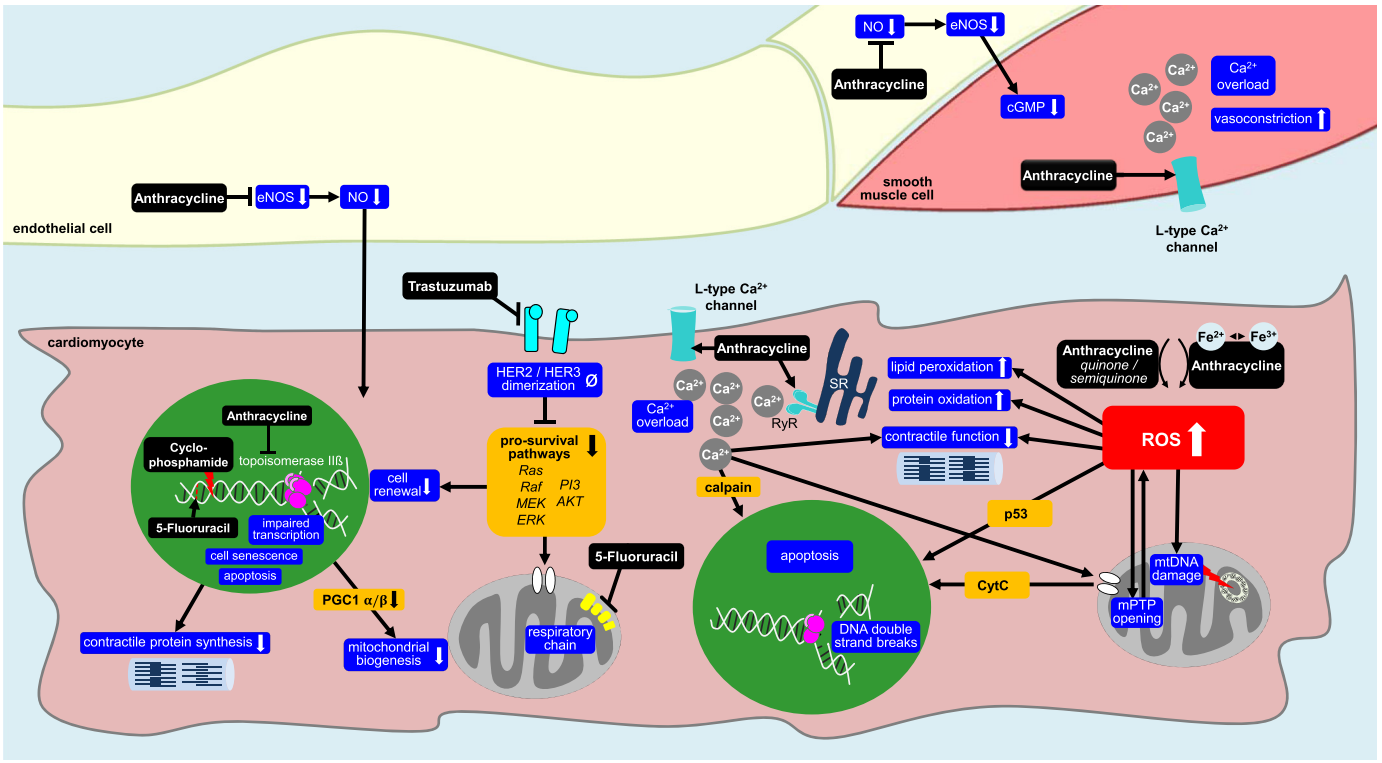

Fig. 1. Molecular/cellular targets of cancer therapy in cardiomyocytes. Classical chemotherapy with anthracyclines has multiple cellular and subcellular targets in the cardiovascular system. In cardiomyocytes, anthracyclines are converted in a redox reduction through several NAD(P)H/H^+-dependent enzymes (anthracycline-quinone to semiquinone). This reaction results in ROS formation, as does the interaction of anthracyclines with ionic iron. Oxidative modification of DNA, proteins, lipids results from ROS formation. Anthracyclines inhibit nuclear topoisomerase IIβ and cause DNA double strand breaks. In consequence, mitochondrial transcription factors (PGC1α/β) are reduced and mitochondrial biogenesis is impaired along with an impaired synthesis of contractile proteins. In mitochondria, anthracyclines through increased ROS formation damage mtDNA and increase opening of the mPTP, thus initiating apoptosis and cell death. Calcium overload results from anthracycline-induced opening of L-Type calcium channels and ryanodine receptors (RYR) of the sarcoplasmic reticulum. In the vasculature, anthracyclines reduce endothelial nitric oxide synthase activity and increase cytosolic calcium in smooth muscle cells, thus favoring vasoconstriction. Inhibition of the HER2 receptor by e.g. trastuzumab decreases a distinct kinase pathway and also increases the formation of ROS. Alkylating agents (e.g. cyclophosphamide) promote ROS formation and DNA damage. Likewise, ROS formation and DNA damage along with endothelial dysfunction and vasospasm result from 5-fluoruracil. (eNOS = endothelial NO synthase, NO = nitric oxide, cGMP = cyclic guanosine monophosphate, Ca^{2+} = calcium, ROS = reactive oxygen species, PGC1α/β = peroxisome proliferator activated receptor gamma co-activator α/β, O_2 = oxygen, RAS = rat sarcoma (protein kinase), RAF = rapidly accelerated fibrosarcoma (protein kinase), MEK = mitogen activated protein kinase kinase, ERK = extracellular signal regulated kinase, PI3 = phosphoinositide 3-kinase, AKT = protein kinase B, Cyt C = cytochrome C, mPTP = mitochondrial permeability transition pore, mtDNA = mitochondrial DNA, RYR = ryanodine receptor, SR = sarcoplasmic reticulum).

result of coronary vasospasm, and possibly also induce acute myocardial infarction and arrhythmias. Cardiotoxicity from antimetabolites involves also ROS formation, mitochondrial dysfunction, lipid peroxidation and DNA damage [57]. Organic nitrates can be used to prevent vasospasm in 5-fluorouracil-treated patients [14].

3.3. Molecular therapies targeting signal transduction

Molecularly targeted therapies interfere with aberrant signaling pathways in the cancer cell or its microenvironment. Single- and multi-kinase inhibitors are selected by their pharmacokinetics and selectivity and by cancer entity/stage [58]. Their cardiotoxic effects result from inhibition of kinase signaling in the vasculature and in the heart. However, their exact cardiotoxic mechanisms are incompletely understood, and methods to predict their cardiotoxicity are currently being evaluated [59].

Several inhibitors of tyrosine kinases involved in VEGF signaling have received approval from regulatory agencies (Supplementary Table 1). These tyrosine kinases regulate angiogenesis, vascular and myocardial function and metabolism. Adverse cardiovascular events from these inhibitors are related to their interaction with these cellular functions. Short-term inhibition of tyrosine kinases exacerbates injury from ischemia/reperfusion [60]. Chronic inhibition of VEGF signaling impairs angiogenesis [61].

Many of the effects of targeted therapies have been related to an inhibition of VEGF receptors and VEGF-related NO downstream signaling in the cardiovascular system. eNOS-phosphorylation and reduced activity go along with increased vascular ROS levels [62]. This contributes to endothelial dysfunction, microvascular injury, vascular stiffness, and finally hypertension [63]. Likewise, VEGF inhibitors may promote thrombosis, eventually resulting in venous and arterial thromboembolic events [64]. Small molecule TKI inhibits several kinases in parallel. It is currently unclear why individual patients respond to TKI medication with cardiotoxicity. To that effect, cell culture models are being tested to identify a patient's individual susceptibility [59]. Finally, TKI-associated inhibition of the platelet derived growth factor receptor (PDGFR) may further explain the development of heart failure in this group of tumor therapeuticals, given that mice lacking PDGFR develop heart failure [65].

Current evidence for cardiotoxicity has been derived from secondary outcomes of studies in cancer patients. The precise nature of adverse events, their frequency, and their potential impact on patient management have recently been summarized [66]. The most frequent cardiovascular adverse events include arterial hypertension and arrhythmia (QTc prolongation) [67]. The risk for myocardial ischemia and stroke is increased up to 2-fold, and there is a trend towards increased arterial and venous thrombotic events. Currently, no guideline recommendation exists for anticoagulation in these patients. The topic of thrombosis

vs. anticoagulation is particularly difficult as VEGF targeted therapies also carry a relevant risk for bleeding [66,68], therefore requiring individual decision making in case either event occurs.

Emerging evidence also points to increased risk of heart failure from VEGF-targeting therapy. The primary recommendation for cancer patients treated with anti-angiogenic agents is therefore to control for cardiovascular risk factors. The efficacy of preventive measures still remains to be evaluated [58]. Tyrosine kinase inhibitors targeting endothelial growth factor receptor (EGFR, e.g. erlotinib in non-small cell lung cancer) may contribute to the development of hypertension, but appear to have less cardiotoxicity [58,59].

Another novel class of targeted therapies is serine-threonine protein kinase inhibitors (e.g. the BRAF [mutated rapidly accelerated fibrosarcoma kinase B] inhibitors dabrafenib and vemurafenib, and the MEK [mitogen-activated protein kinase kinase] inhibitors trametinib and cobimetinib). These agents have individually and in combination improved survival in patients with metastatic melanoma. In 40% of all melanoma patients, somatic $BRAF^{V600}$ mutations indicate a targetable oncogenic dependency [69]. Treatment-associated complications with BRAF and MEK inhibitors occur particularly with combination therapies [70]. Adverse cardiovascular events have been related to protein kinase inhibition in cardiomyocytes, e.g. QTc prolongation with dabrafenib and heart failure with trametinib.

BRAF/MEK inhibitors target a central signaling pathway with multiple targets and functions [71]. A final signaling step is ERK which in turn targets >100 substrates involved e.g. in cardiac metabolism and growth [72,73]. The toxic effects of BRAF/MEK inhibitors and their downstream events have not been analyzed yet in great detail in preclinical studies. Exact metrics of incidence of such toxicities from long-term studies are missing. The efficacy of established heart failure therapies, including ACE inhibitors and β blockers in this specific situation, remains to be evaluated.

3.4. Immune checkpoint inhibitors (ICI)

In addition to cytotoxic chemotherapy and small molecule inhibitors a new class of agents, ICI, has recently emerged as another pillar of systemic cancer therapy. Approved drugs include antibodies directed against programmed cell death receptor 1 (PD-1), programmed-cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) [74].

T-cells interact with target tissues through multiple receptor–ligand interactions. PD-1 on T-cells and its ligand PD-L1 on cancer cells as well as microenvironmental cells are prototypic regulators of immune activation. PD-1-related signaling promotes self-tolerance and prevents autoimmunity by locally suppressing the immune system through anergization and apoptosis of antigen-specific T cells and diminished apoptosis of regulatory T cells [75]. Tumor cells may express PD-L1, and the interaction with PD-1 on T-cells results in immune evasion. [76,77] Clinically, ICI therapy can induce a fulminant lymphocytic myocarditis with high mortality. An autoimmune reaction against myocardial antigens is the assumed underlying pathomechanism in these patients.

Based on early signals of clinical activity, which triggered pivotal trials, ICI were first approved in cutaneous malignant melanoma, a disease, which is practically insensitive to cytotoxic agents. Today ICI are standard of care in the management of metastatic melanoma and have also moved into adjuvant therapy for high-risk populations. Due to their unique mode of action, ICI are potentially applicable in numerous cancer entities, and thus have been studied in multiple clinical trials. Currently, ICI are approved standard of care in patients with metastatic non-small cell lung cancer, bladder cancer, renal cell cancer, head and neck cancers, Hodgkin's disease, and Merkel cell cancer. More entities are continuously added to this list. Interestingly, FDA has also granted entity-independent approval for PD-1 antibodies in patients with microsatellite-instable cancers. The power of ICI is their potential to induce long-term remissions and disease-control in patients with metastatic cancers who previously had very limited life expectancy. Unfortunately only an imprecisely defined subgroup of cancer patients derives this benefit so far. However, considerable numbers of patients already enjoy long-term survival in cancers that are frequently associated with significant cardiovascular comorbidities (e.g. lung cancer, bladder cancer). These patients may experience not only early but also late toxicities from these new therapeutic immune interventions. Adverse events associated with ICI range from arrhythmias to myocarditis (Supplementary Table 1) [5,6,74,77–79]. Although infrequent, cardiotoxicity may be life threatening. The molecular basis of these adverse events remains incompletely understood, but immune mechanisms are clearly expected. The development of auto-reactive antibodies against cardiomyocytes (e.g., contractile elements) has been suggested but not confirmed in human biopsies [78,80].

4. Diagnosis of cardiotoxicity

Currently the main strategy in cardio-oncology is early detection and treatment of cardiovascular disease [81]. Risk factors predispose to cardiotoxicity and/or result from cancer therapy. The detection of subclinical structural heart disease is more challenging. There are currently no data and no general recommendations for the use of biomarkers in cardio-oncology patients, but troponin and brain natriuretic peptide (BNP) levels are routinely measured in cardio-oncology centers. In tumor patients receiving chemotherapy, troponin elevation has been used to reflect the susceptibility to cardiomyopathy-inducing drugs, particularly anthracycline therapies [16,82,83]. Indeed, the combined use of troponin measurement and echocardiography has been superior in the diagnosis of cardiotoxicity over echocardiography alone [84]. Future trials must assess the value of troponin in larger cancer cohorts for the exact definition of biomarker distribution and cut-off levels. Currently, troponin should be assessed in patients before and during anthracycline therapy, during checkpoint inhibitor medication, and whenever ischemic heart disease is suspected.

Echocardiography, particularly 2D assessment of left ventricular ejection fraction, remains the standard method for the evaluation of cardiac function, but 3D, when available, is more precise [8]. Cardiotoxicity is defined as a decrease in 3D ejection fraction by 10% to a level below 50% [3]. Speckle tracking global longitudinal strain (GLS) imaging has comparably high specificity and sensitivity, low intra- and inter-observer variability, and provides comparable results to magnetic resonance imaging (MRI) [84]. In patients undergoing bone marrow transplantation for either non-Hodgkin's lymphoma or leukemia, early GLS changes predict changes in ejection fraction after 1 year [85]. Comparable results were obtained in breast cancer patients under combined treatment with anthracycline and trastuzumab [86]. MRI remains the gold standard for the quantification of cardiac dimensions and ventricular function, but is often only used as a secondary option – mainly in patients with poor echocardiography windows or inconclusive results.

5. Spectrum of cancer therapy-related cardiovascular disease

Therapeutic recommendations are largely derived from AHA/ACC/ESC cardiovascular guidelines rather than from prospective clinical cardio-oncology trials. Specific cardioprotective approaches to prevent cardiotoxicity in children and adults undergoing cancer treatment are currently tested, including exercise or remote ischemic preconditioning [87] (e.g. NCT03166813, NCT02471885, NCT01621659, NCT03089502). Currently available data suggest that cardiotoxicity is potentially reversible for several therapies [14,15]. Definitions of adverse cardiovascular events from cancer drugs rely on 'Common Terminology Criteria for Adverse Events' by the National Cancer Institute (CTCAE, ctep.cancer.gov.; Supplementary Table 2). Most patients in cardio-oncology units present with heart failure but the complete spectrum of cardiotoxicity must be considered [88].

5.1. Hypertension

Hypertension develops in nearly one third of cancer patients, often over the first few weeks of cancer therapy, and may limit prognosis [15]. Established and novel cancer therapies have been associated with increased risk of hypertension (Supplementary Table 1). Hypertension develops in nearly one third of cancer patients, often over the first few weeks of cancer therapy, and may limit prognosis [15]. VEGF and proteasome inhibitors pose the highest risks, and this association is probably related to impaired endothelial function, reduced NO formation, and vasoconstriction [66,68]. Post-hoc analyses have even suggested the development of hypertension as a pharmacodynamic parameter reflecting effective anti-angiogenic cancer therapy [89]. The diagnosis is based either on office of ambulatory tests, and the severity of hypertension is then graded (Supplementary Table 2). The 2017 AHA guidelines have introduced very strict cut-off values (>120/80 mm Hg), while the 2018 ESC guidelines continue to define hypertension with the conventional limits (≥140/90 mm Hg). Patients under VEGF targeted therapies should be particularly monitored during the first cycles, while other therapies may promote hypertension over the entire course of treatment. Upon diagnostic follow-up, hypertension may be caused not only by cancer therapy per se but also by fluid overload or pain. The current ESC guidelines recommend ACE inhibitors and calcium antagonists as first line option [90]. Many patients will require combination therapies to achieve sufficient blood pressure control. Of note, experimental evidence supports an anti-cancer effect of ACE inhibitors [91].

5.2. Venous thromboembolism

Cancer patients are at risk for deep vein thrombosis and pulmonary embolism, and this risk has been related to the tumor itself and to cancer therapies. Patients with thromboembolic events have a limited prognosis [92,93]. The incidence of thromboembolism depends on the particular malignancy and the therapeutic strategy, but is generally increased during the first 6 months of cancer therapy [94]. Many classical and novel therapies have been associated with venous thromboembolism [95]. The underlying mechanisms (e.g. reduced endothelial function in drugs targeting VEGF), however, remain incompletely understood. Compression ultrasound and CT are the standard imaging tools for diagnosis. Low molecular weight heparin or unfractionated heparin is given for the prevention of thromboembolism or in established thromboembolic disease according to concurrent guidelines [96]. As long as cancer is active in patients, anticoagulation should be continued. Low molecular weight heparin is preferred for long-term treatment, at least if clinically feasible (e.g. platelet count > 50,000/μl, absence of life-threatening bleeding complications, preserved renal function). Clinical adherence to this recommendation is, however, low. Data on the use of direct oral anticoagulants (DOACs) are limited. Two recent trials testing edoxaban and rivaroxaban in larger cohorts of cancer patients confirmed their non-inferiority to standard therapy [97,98]. At this point, data for the other two approved DOACs are pending, and a general recommendation for this class of agents can therefore not be given.

5.3. Coronary artery disease

During the course of cancer therapies, patients are at particular risk to develop progression of pre-existing or development of de novo coronary artery disease. Coronary artery disease manifests itself as stable angina or acute coronary syndrome albeit with arterial thrombus formation during active cancer therapy or even years thereafter. This also applies to the development of acute cerebrovascular events [3]. Patients with cancers associated with smoking (e.g. lung cancer, bladder cancer, head and neck cancers) have more frequently also coronary artery disease. Careful evaluation of the patient's individual and family history should be performed before any cancer therapy. Coronary artery disease may result from accelerated atherosclerosis (radiation), coronary endothelial dysfunction, arterial thromboembolism (e.g. VEGF inhibitors), and coronary vasospasm (e.g. 5-fluoruracil, Supplementary Table 1) in combination with the systemic inflammation resulting from cancer. Some cancer drugs (e.g. tamoxifen in breast cancer) appear to have beneficial effects on ischemic heart disease particularly when compared to aromatase inhibitors [99]. However, cancer patients have been largely excluded from clinical trials on acute and chronic coronary artery disease. Current evidence is therefore limited and patients largely require individualized treatments due to e.g. frailty, clinical need for cancer therapy due to high symptom burden, low platelet counts and access site complications. Acute chest pain requires diagnostic follow-up according to current guidelines, including percutaneous coronary intervention (PCI) and dual anti-platelet therapy. Interventional procedures should be individually tailored in close interaction with the oncologist. Anti-platelet therapy is particularly problematic when myelosuppressive therapies with resulting low platelet counts are planned. In the absence of prospective data, catheterization and dual antiplatelet therapy appear feasible in patients with platelet counts > 30,000/μl [14]. Most PCI procedures can be performed safely with platelet counts of 40–50,000/μl. Of note, novel drug eluting stents may provide the opportunity for shorter dual antiplatelet therapy. Radial access is preferred, but a femoral approach can be considered in patients with a history of multiple arterial lines or in breast cancer patients following mastectomy. Calcium channel antagonists or organic nitrates can be used to prevent vasospasm [3].

5.4. Valvular heart disease

Aortic and mitral valve disease may develop as late toxicities from radiation and result in stenosis or regurgitation [100]. Long-term cancer survivors (>10 years) are at particularly high risk. Clinical and echocardiography assessment is therefore recommended in the long-term follow-up of these patients. Treatment strategies must consider comorbidities and clinical status.

5.5. Heart failure

Clinical signs of heart failure include dyspnea, edema and fatigue. Anthracyclines and HER2-targeting agents (e.g. trastuzumab, lapatinib) are widely recognized to induce potentially irreversible heart failure [1]. We have therefore outlined a treatment algorithm for the assessment and treatment of heart failure, notably in a breast cancer cohort of our center's cardio-oncology unit. Many other agents can induce reversible or irreversible heart failure (Supplementary Table 1) through yet incompletely characterized mechanisms [14]. Diagnosis of heart failure is based on patient history, clinical examination, biomarkers (NT-proBNP, troponin) and echocardiography. Therapy follows current AHA/ACC/ESC guidelines in order to help patients complete their cancer therapy and to reduce morbidity and mortality.

5.6. Arrhythmias

Arrhythmic events during cancer therapy include the complete spectrum from bradycardias to tachyarrhythmias [3,15]. The underlying cause may be a specific agent (e.g. atrial fibrillation during ibrutinib therapy [101]) or multi-faceted (electrolyte imbalance, fluid overload, QT prolongation, co-medication, tumor infiltration of the heart). The incidence of arrhythmias increases with advanced cancer stages, age, sepsis and pain [15]. Targeted inhibitors of signal transduction may induce arrhythmias, however prevention and treatment has not been systematically tested [66]. Therefore, therapy must follow current guidelines, but discussion in multidisciplinary teams with cardiologists and oncologists is advised, including correction of electrolyte imbalance, treatment of sepsis, use of antiarrhythmic drugs and anticoagulation. Of

note, standard scoring systems and pharmacological approaches have not been tested in cancer patients, including the need for anticoagulation.

6. Diagnostic and therapeutic algorithms for specific cardio-oncology patients

Diagnosis and treatment algorithms in cardio-oncology are incomplete and largely based on expert consensus. Below, we discuss specific strategies for three typical cancer cohorts, which frequently report to our and other cardio-oncology units. This includes patients treated with cytotoxic chemotherapy including anthracyclines, patients receiving targeted therapies and the growing cohort of cancer patients under ICI therapy.

6.1. Breast cancer patients undergoing classical chemotherapy

Breast cancer is the most common cancer in females, and thus breast cancer patients comprise the largest group of cardio-oncology patients. Generally, breast cancers have a favorable stage-dependent prognosis, with 5- and 10-year survival rates of 89% and 83%, respectively [102]. Most patients live for 20 more years or longer. With increasing numbers of breast cancer survivors, cardiovascular diseases secondary to cancer therapy become more relevant, sometimes many years after therapy [103,104]. A systematic analysis of >1.2 million breast cancer survivors revealed an 1.9-fold increased risk of death from cardiovascular disease over that in an age-matched population [103]. Risk factors for heart failure include anthracyclines, HER2-targeting agents, and/or radiation. The risk for the development of heart failure is not limited to the period of treatment but sustained for decades following therapy, and cardiovascular risk factors augment this risk [105]. The prevention of cardiovascular disease in breast cancer patients is based on an elaborate preselection of patients and risk-reducing treatment protocols, treatment of cardiovascular risk factors and early detection and treatment of adverse effects. Fig. 2 proposes an algorithm for the management of these patients based on recent recommendations from cardiological [3,8] and oncological [6,106] societies. After assessment of baseline cardiac function using cardiovascular history and echocardiography, patients with normal baseline ejection fraction are monitored over the following months for early signs of cardiotoxicity (e.g. every CTCAE grade for heart failure, Supplementary Table 2). Follow-up is recommended 6–12 months after completion of chemotherapy [6,106]. Long-term survivors are re-evaluated for cardiovascular risk factors and signs of cardiovascular disease (hypertension, coronary artery disease, heart failure and/or arrhythmias) at 5-year intervals [14,15]. Chemotherapy protocols avoiding high-risk agents are considered for patients with pre-existing moderate-to-severe heart failure, including use of pegylated liposomal doxorubicin or concomitant use of dexrazoxane. Dexrazoxane was developed to protect from anthracycline-induced cardiotoxicity by reduced ROS formation [4]. Dexrazoxane is now increasingly used for cardioprotection.

Treatment of evident cardiotoxicity must be initiated as early as possible – ACE inhibitors (or angiotensin receptor type II subtype 1 receptor [AT1] antagonists) and β blockers are proposed [3]. Yet, even though combination therapy is in line with current heart failure guidelines [107], this approach has only been tested in few oncological studies. The PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) trial was a randomized, controlled study with a 2 × 2 factorial design using the AT1 blocker candesartan and the β blocker metoprolol. The decline in ejection fraction in the placebo group was moderate, but candesartan reduced the incidence of heart failure [108]. In the CECCY trial (Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity) the β blocker carvedilol failed to prevent a decline in left ventricular ejection fraction. However, troponin levels and diastolic dysfunction (secondary outcomes) were reduced in β blocker recipients [109]. The OVERCOME (Prevention of Left Ventricular Dysfunction with Enalapril and Carvedilol in Patients Submitted to Intensive Chemotherapy for Malignant Hemopathies) trial in leukemia patients revealed a small benefit of this combination therapy as secondary outcome [110]. Several randomized, placebo-controlled studies analyzed the effects of ACE inhibitors/AT1 antagonists or β blockers separately in cancer patients. Until further conclusive evidence is available, breast cancer patients with heart failure are recommended to receive treatment with ACE inhibitors and β blockers.

6.2. Melanoma patients receiving targeted therapies (BRAF/MEK inhibitors)

A recent post-hoc analysis revealed improved survival with BRAF/MEK inhibition at least in the first months of treatment in advanced melanoma [111]. The majority of patients selected for BRAF/MEK inhibition with trametinib/dabrafenib experience adverse effects, but mostly to a minor extent [70,112]. Heart failure at all CTCAE grades from BRAF/MEK inhibitors occurred in up to 12% of patients [113]. Baseline and follow-up assessment of ejection fraction is essential (Fig. 3). For patients with moderate-to-severe reduction in baseline ejection fraction, alternative therapies for melanoma can be considered if possible. Prolongation of QTc time is the second most frequent adverse cardiovascular event in patients with BRAF/MEK inhibition. If baseline QTc remains high despite optimal electrolyte levels (specifically magnesium and potassium), alternative cancer therapies should be considered, i.e. ICI in the case of melanoma. Therapy should be terminated whenever QTc increases by >60 ms to a level above 500 ms. Given the anecdotal evidence regarding handling of cardiotoxicity in BRAF/MEK treated patients, no specific therapy for cardiomyopathy can be recommended at this point.

6.3. Treatment strategies using immune checkpoint inhibitors

ICIs are used in multiple malignant diseases. However, along with their incremental use and improved patient survival, adverse cardiovascular effects are increasingly observed [74]. In particular, fatal myocarditis has been recently reported. Initially, its incidence appeared low, but recent reports suggest myocarditis as defined by AHA guidelines in approximately 1.1% of patients.

Given the fulminant nature of such immune toxicities, early detection is mandatory (Fig. 4) [114]. We propose an algorithm based on recent recommendations from the American Society of Clinical Oncology: [114] Echocardiography and troponin level should be assessed within the first month of treatment. Any signs of cardiotoxicity should also be evaluated promptly (troponin, NT-proBNP, chest X-ray, echocardiography, MRI). Positron emission tomography to visualize inflammation of the myocardium is probably of additional value if myocarditis is suspected. In cases of severe and rapid progression of heart failure, an endomyocardial biopsy should be taken [107]. If myocarditis is suspected, ICI should be paused at any clinical grade (Supplementary Table 2). Therapy should be permanently terminated when myocarditis is confirmed (MRI or biopsy) and prolonged immunosuppressive therapy should be initiated [115]. Glucocorticoids are considered as first-line treatment (initially 1–2 mg/kg prednisone, alternatively 1 g methylprednisone in non-responders) [114], and inhibitors of tumor necrosis factor α are an option if there is no response to steroids [115]. Patients should be transferred to a coronary care unit for further follow-up.

Currently, no general guideline recommendations exist regarding a re-challenge with ICI in case myocarditis is ruled out. Confirmed myocarditis, advanced conduction disease and ventricular tachycardia will require permanent ICI termination. It has, however, recently been argued that in patients with acute myocardial infarction, Takotsubo syndrome, atrial fibrillation as other potential causes for troponin increases under ICI, therapy may be re-initiated when myocarditis has been ruled out and the patient is stable [116]. Close monitoring is

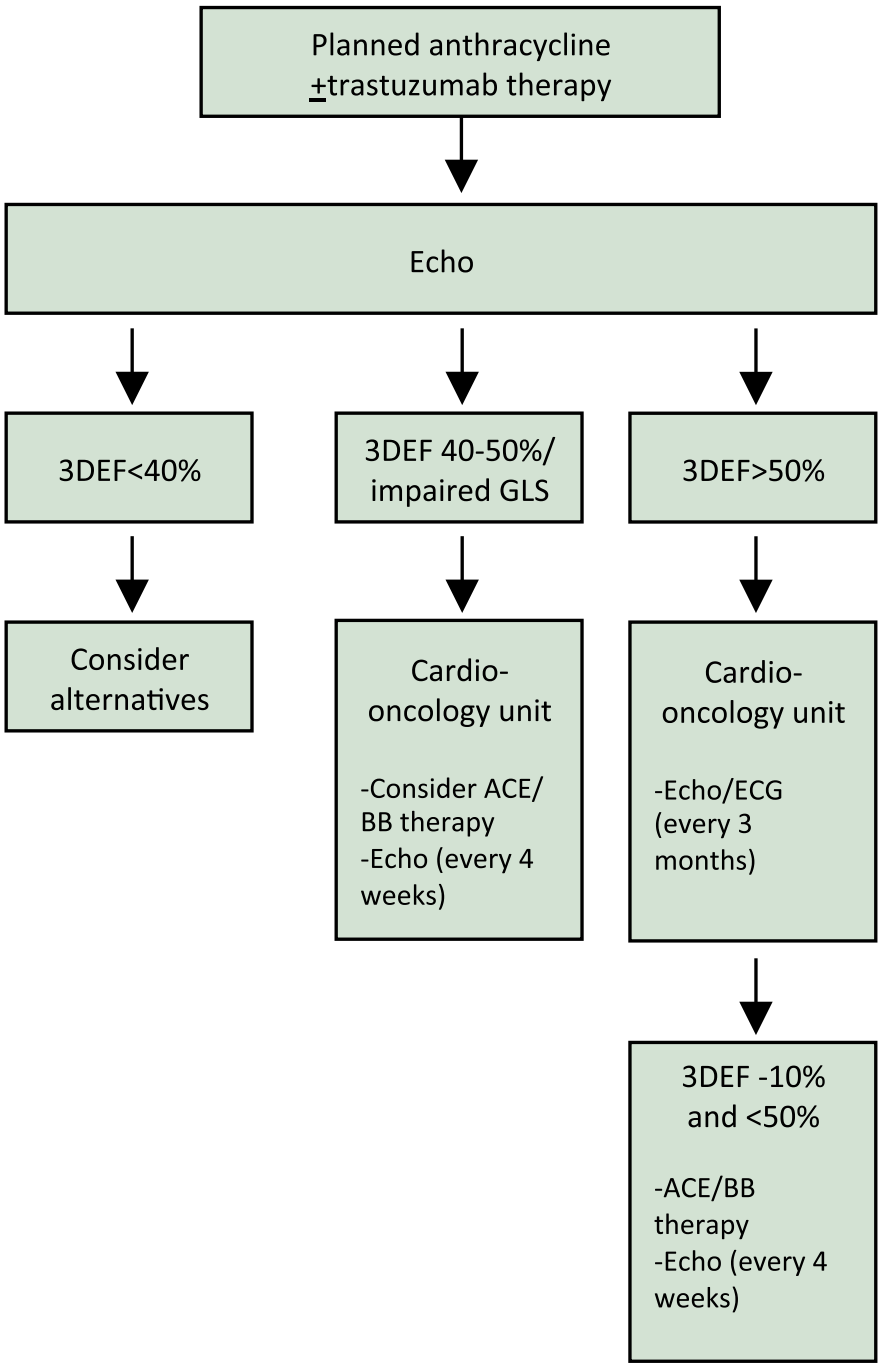

Fig. 2. Algorithm for the assessment of patients receiving classical chemotherapy. Initial evaluation is recommended in all patients scheduled for heart failure-inducing agents, particularly anthracyclines and HER2-targeting agents such as trastuzumab. Current cut-off values for ejection fraction (EF; as measured in 3D) are set to 50%. Cardiotoxicity is defined when EF declines by >10% to values below 50% or if GLS is impaired by >15%. Treatment is recommended with ACE inhibitors and ß-blockers, but evidence from randomized trials is scarce. Heart failure with reduced ejection fraction is defined by EF below 40%. Cessation or alternative therapies are then recommended, including lower doses or second line therapies. However, individual treatment decisions are required since otherwise many patients would be excluded from highly effective therapies (3D EF = 3-dimensional ejection fraction, ACE = ACE inhibitor, BB = β blocker, echo = echocardiography. ECG = electrocardiogram, GLS = global longitudinal strain).

mandatory. For acute coronary syndromes, a 1 month interruption of ICI therapy has been proposed [116].

7. Development and standard procedures of a cardio-oncology unit

The cardio-oncology unit of the West German Heart and Vascular Center, notably its Department of Cardiology and Vascular Medicine treats patients in a multidisciplinary approach together with the departments and institutes of the West German Cancer Center, including the Departments of Medical Oncology, Hematology, Bone Marrow Transplantation, Radiation Oncology, Gynecology and Dermatology. The Department of Cardiology and Vascular Medicine is a tertiary care center with certified chest pain, coronary care, heart failure and intensive care units. The cardio-oncology service has established a close collaboration with the imaging institutes (radiology and nuclear medicine). All state-of the heart diagnostic and therapeutic tools are available, including PET/CT and PET/MRI. An institutional communication has been established through an online system for consultants, and daily

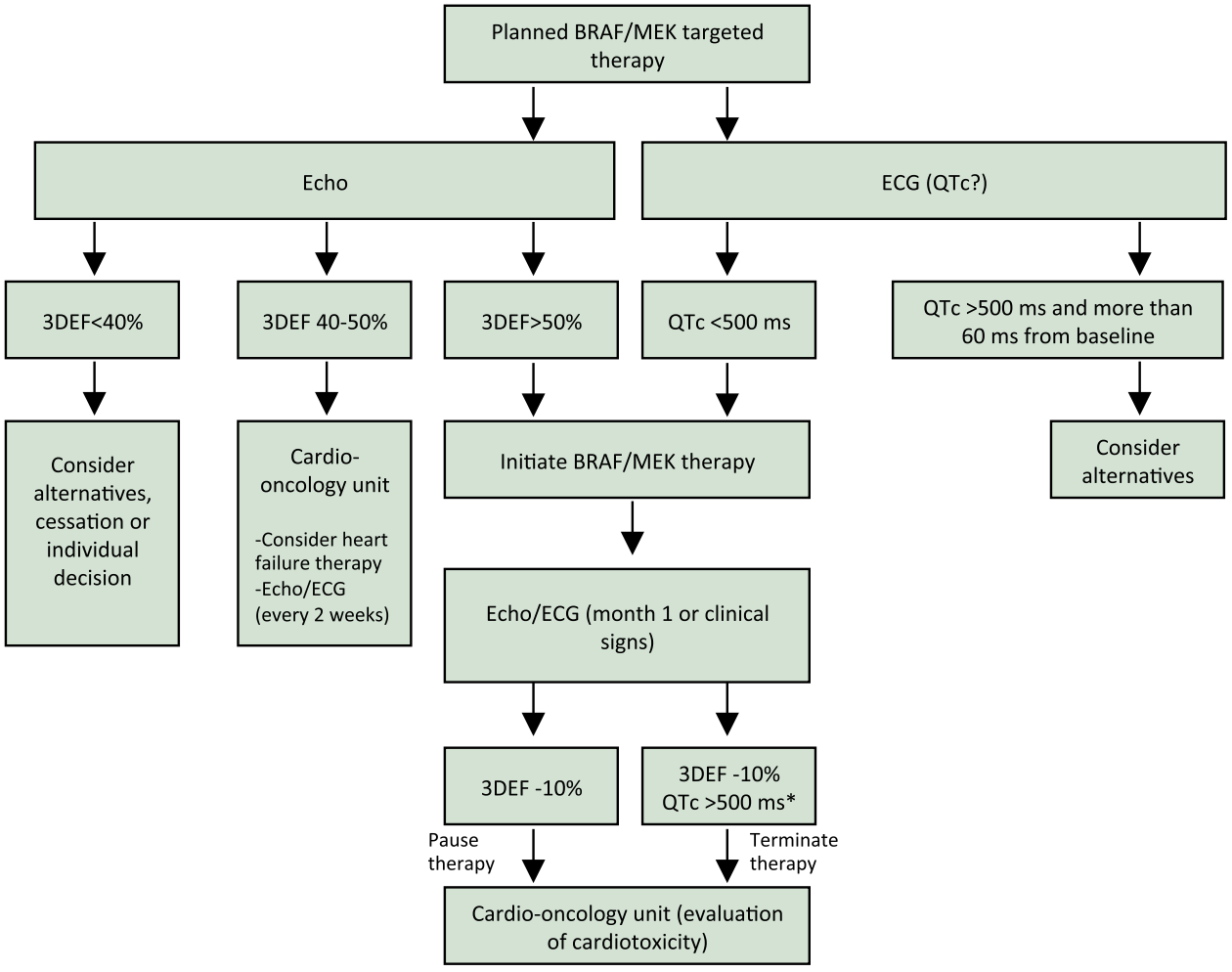

Fig. 3. Recommended algorithm for the evaluation of patients with targeted therapy. Adverse cardiovascular effects from BRAF/MEK inhibition include heart failure and QTc prolongation to a level with increased risk of torsades des pointes. 3D ejection fraction is monitored before and during therapy. A decline in EF by 10–20% warrants an interruption of therapy with evaluation of heart failure medication. If heart failure persists or EF remains reduced by 10–20%, therapy with BRAF/MEK should be re-evaluated and discussed. However, therapy termination may exclude patients from this therapy and its benefits. Individualized decisions by the multi-disciplinary cardio-oncology team and repeated echocardiographic assessment are therefore required. Persistent QTc prolongation may require BRAF/MEK withdrawal (*temporary QTc elongation should be treated by correction of magnesium and potassium levels and then re-evaluated, ECG = electrocardiography. Echo = echocardiography 3DEF = 3-dimensional ejection fraction).

consultations are performed. With support from the University Hospital, experimental and clinical research trials have been initiated in the cardio-oncology unit. The education of personnel is provided through regular case conferences and tutorials. Together with the oncology departments, standard operating procedures have been implemented. Breast cancer patients scheduled for anthracycline therapy, myeloma patients, and patients receiving ICI are among the most frequently referred to the cardio-oncology service.

Breast cancer patients receiving anthracyclines (in conjunction with HER2-inhibitors) are monitored at the cardio-oncology unit at three time-points: before the initiation of chemotherapy and following three and six months. The gynecology department automatically refers all respective patients following a tumor board decision. Each patient receives an echocardiography, including 3DEF and GLS, blood test for troponin, NT-proBNP, lipid profile and ECG. All parameters are tested during follow-up visits for signs of subclinical cardiotoxicity [16,82,117,118]. Whenever signs of cardiotoxicity become evident (elevated troponin, impaired LVEF/GLS) the interruption of chemotherapy is discussed with the treating oncologist. Beta-blockers and ACE-inhibitors are routinely used to treat toxic cardiomyopathy. Statins are recommended according to guideline recommendations. The clinical status, including echocardiography, is re-assessed at least every four weeks in patients with cardiotoxicity. Additional consultations may be necessary upon signs of cardiotoxicity, including: angina, dyspnea, arrhythmia including QT > 500 ms, pericardial effusion, edema, congestion, acute coronary syndrome, hypertension, hypotension and syncope. Severe heart failure and cardiogenic shock are occasionally observed due to anthracycline therapy. Left ventricular assist devices (Impella, LVAD) have been implanted in selected cases for temporary or permanent support. We recommend that all breast cancer survivors are re-evaluated by a cardiologist in case of a planned pregnancy.

Myeloma patients are referred to the cardio-oncology service from the hematology department. Proteasome inhibitors, including bortezomib and carfilzomib, come along with an increased risk of heart failure. Due to the high number of referred patients, we routinely assess all patients before and six months after initiation of therapy. A clinical registry has been established for the systematic assessment of clinical status and vascular and left ventricular functions. We recommend ambulatory blood pressure tests in all patients to monitor for possible hypertension or hypotension. In cases of cardiotoxicity, beta-blockers and ACE-inhibitors can be given but may worsen hypotension. Mineral corticoid receptor antagonists are an alternative option.

ICI may induce multiple cardiotoxic adverse events, including myocarditis, pericarditis, pericardial effusion, acute coronary syndromes and advance conduction abnormalities (second and third degree AV Block). Baseline assessments, including clinical history, examination and ECG

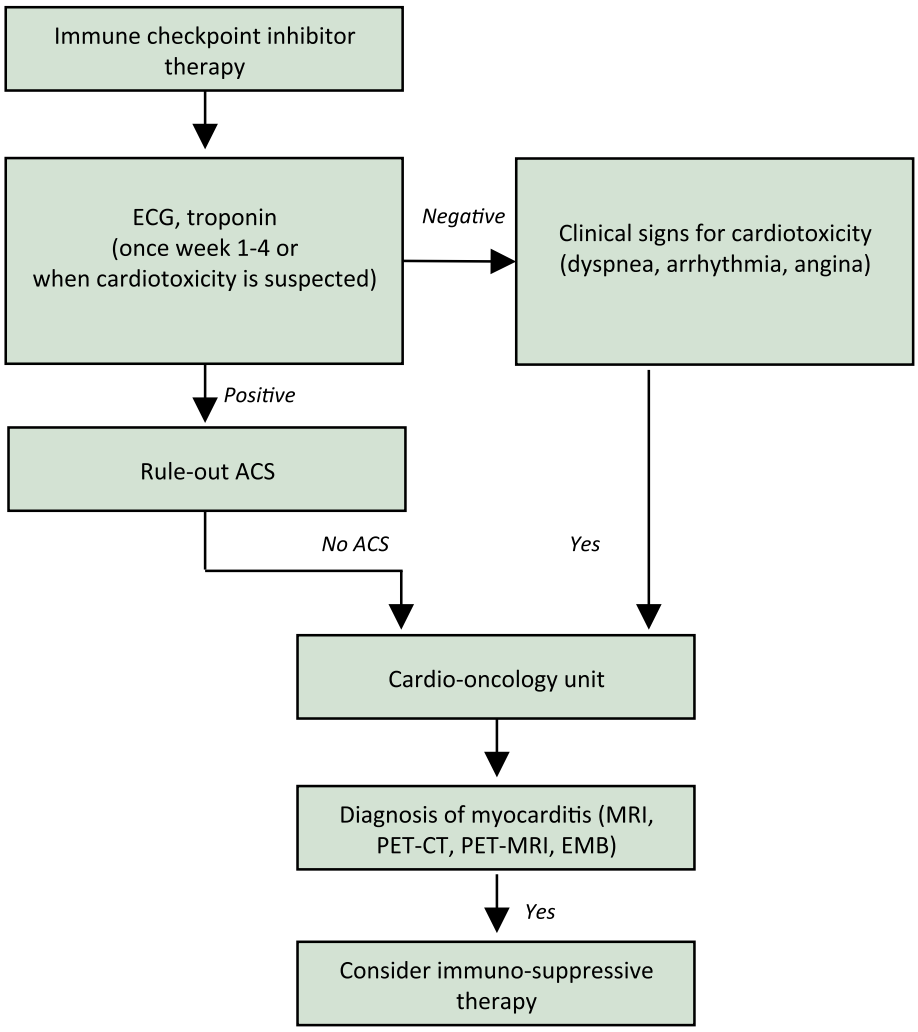

Fig. 4. Recommended algorithm for the evaluation of patients with immune checkpoint inhibitor therapy. A cardiac reaction to immune therapy is a rare, but fulminant condition. Clinical signs are dyspnea, arrhythmia (particularly advanced conduction disease) and angina. Electrocardiography (ECG) and troponin (high-sensitive troponin I or T) measurement identify early stages of such myocarditis and are recommended in weeks 1–4 of treatment or when cardiotoxicity is suspected. An acute coronary syndrome is evaluated according to current guidelines and may require coronary angiography. Persistent symptoms should be evaluated despite negative troponin and ECG in cardio-oncology units. Holter-ECG and imaging, including echocardiography, magnetic resonance imaging, possibly in combination with positron emission tomography, are helpful to confirm myocarditis. Severe cases of heart failure with rapid progression should be evaluated by endomyocardial biopsy to confirm immune therapy-related adverse events and exclude other causes. Glucocorticosteroids are the first choice treatment [11]. (ACS, acute coronary syndrome, CT = computed tomography, ECG = electrocardiogram, EMB = endomyocardial biopsy, PET = positron emission tomography, MRI = magnetic resonance imaging).

are performed by the oncologists. The patients are served by clinical consultation together with ECG and troponin tests once in the first four weeks of treatment. In cases of signs of dyspnea, angina and arrhythmia or positive ECG/troponin tests, patients are referred to the cardio-oncology unit via the online system. If myocarditis is suspected, we discuss termination of ICI therapy until myocarditis is ruled-out definitely. The further work-up includes echocardiography and nuclear imaging (PET/CT or PET/MRI) and in indecisive cases endomyocardial biopsy. Proven myocarditis is treated with 1 mg/kg prednisone as first-line option. Whenever myocarditis has been ruled-out, ICI is only re-challenged after consultation with the oncologist and repeated testing at least once four weeks after the initial visit.

8. Adult survivors of childhood, adolescent and young adult malignancies

Advances in the treatment of childhood, adolescent and young adult (CAYA) malignancies have yielded substantially increased survival [119,120]. As adults, many of these patients experience premature cardiovascular disease. By the age of 35 years, cancer recurrence and cardiovascular disease increase morbidity and mortality as compared to age-matched controls [11,121]. A 15-fold increased risk of heart failure and a 7-fold increased of premature cardiac death were reported [120]. Cardiovascular morbidity and mortality are particularly associated with anthracycline-based chemotherapy and chest irradiation [12,18,119,122]. More than 20 years after therapy, nearly 40% of patients have coronary lesions as detected by computed tomography angiography [123]. Whether these dramatic figures still hold true with current highly sophisticated treatment planning and radiotherapy options is still an open question. Symptoms may often be uncharacteristic and include fatigue, palpitations, and syncope. Classical signs of structural heart disease, including exertional dyspnea and angina, may be absent. Therefore particularly careful examination of childhood cancer survivors is warranted. The development of cardiovascular risk factors must be closely monitored beginning two years after exposure to cancer therapies [119,120]. According to current recommendations [119,120], symptomatic patients should be referred to cardiological evaluation. Asymptomatic patients are to be monitored every 5 years by clinical assessment, electrocardiography and/or alternative imaging modalities. When subclinical signs of cardiovascular disease are detected, patients

should be referred to a cardiologist [120]. After 10 years, stress testing should be performed even in asymptomatic cancer survivors (echocardiography, MRI, scintigraphy) [15].

9. Conclusions and perspective

Due to better tolerability and precision of modern cancer therapies, more patients with cardiovascular risk factors undergo potentially cardiotoxic cancer treatments. Moreover, survival rates of cancer patients have generally improved, and the introduction of modern therapies directed against specific molecular targets and of immune checkpoint inhibitors has provided long-term disease control even in advanced or metastatic cancer populations. Hence, prevention, monitoring and early treatment in particular of late toxicities associated with cancer therapy are of growing importance. The characterization of cardiotoxicity from many specific cancer treatments is incomplete. This is particularly true for the plethora of novel cancer agents that were clinically introduced during the past decade. Adequate detection of early and subclinical effects requires attention to clinical signs and symptoms along with biomarkers and imaging. Specific treatments of cardiovascular complications in oncology are not yet established.

General physicians and cardiologists are confronted with an increasing number of patients surviving cancer treatment or receiving long-term cancer therapy. A broad diversity of their symptoms and diseases, ranging from acute coronary events to chronic heart failure, is encountered. Careful examination of these patients is best realized in close cooperation between cardiologist and oncologist, and by dedicated cardio-oncology teams that are established in comprehensive cancer centers [58,78,112,115,124]. Cardio-oncology units provide diagnosis and treatment of acute and chronic cardiotoxicity for cancer patients. As clinical presentation and underlying heart disease in cardio-oncology patients may differ from those in canonical cohorts specific curricula must be developed for cardio-oncologists. Interaction must be established between the cardio-oncology unit and the local imaging center, the emergency department, and the intensive care unit. Given the paucity of data for long-term cancer survivors and specific treatment options, appropriate pathways of patient management must be elaborated and established. Preventive, diagnostic and therapeutic algorithms must be continuously re-evaluated in interdisciplinary cardio-oncology boards. Ultimately, the cardio-oncology team must balance between effective cancer therapy and cardiotoxicity. Of note, direct and indirect complications from cancer per se, including venous thromboembolism, pericardial effusion and tamponade, superior vena cava syndrome, constrictive pericarditis and valvular heart disease are beyond the scope of the present review but can often not be distinguished from cardiotoxic effects of cancer therapy.

Cancer survivorship programs continuously monitor patients for morbidity and mortality and aim to characterize the long-term success in relation to the quality of life. Ideally, these programs assess cardiovascular complications on a patient- and physician-reported basis [125]. Current deficiencies in such programs include inconsistent structures, lack of evaluation, missing risk factor and outcome data, and socioeconomic costs [126]. A better mechanistic understanding of the molecular and cellular targets of classical chemotherapy and novel cancer therapies is needed to develop more specific prevention and treat.

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Appendix A. Supplementary data

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