Cardio-Oncology: A New Discipline in Medicine and Its Relevance to Hematology

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Abstract

Cardio-oncology, a burgeoning subspecialty, addresses the complex interplay between cardiology and oncology, particularly in light of increased cardiovascular (CV) disease mortality in cancer patients. This review provides a comprehensive overview of cardio-oncology with a focus on the therapies used in hematological malignancies. We explore the bidirectional relationship between heart failure and cancer, emphasizing the need for collaborative care. The review discusses risk stratification, highlighting the importance of baseline CV risk assessment and personalized surveillance regimens. Primary and secondary prevention strategies, including pharmacological interventions, are outlined. The review also delves into the cardiotoxicity associated with hematological cancer therapies, focusing on anthracyclines, Bruton kinase inhibitors, BCR-ABL tyrosine kinase inhibitors, CAR-T cell therapy, immune checkpoint inhibitors, multiple myeloma treatments, and hematopoietic stem cell transplantation. We then highlight the high risk of venous and arterial thromboembolisms in cancer patients and the challenges of anticoagulation management in cardio-oncology. Finally, the review touches on the importance of long-term follow-up and appropriate screening in cancer survivors at high risk of CV morbidity and mortality, based on their CV risk profile and the type and dose of cardiotoxic therapies they received such as anthracyclines or high radiation doses.

Keywords

- cardio-oncology
- cardiotoxicity
- thrombosis
- prevention

Introduction

In the rapidly evolving landscape of modern medicine, the crossroads between cardiology and oncology have become increasingly pronounced. As advancements in cancer treatments have ushered in a new era of prolonged survival for many patients, this victory has been tempered by a recognition of unintended consequences: cancer patients have an on-average two to six times higher cardiovascular disease (CVD) mortality than the general population.[1–3] This difference remains and in some cases even increases years after the end of cancer therapy.[1–3] The intricate balance between curing malignancies and preserving cardiovascular (CV) health has necessitated a multidisciplinary approach, leading to the birth of "cardio-oncology." This emerging subspecialty seeks to harmonize the objectives of both fields, ensuring that the quest to eradicate cancer does not come at the undue expense of the heart. The ever-increasing complexity and interdependence of oncology, hematology, and cardiology necessitates the creation of collaborative care teams to optimize outcomes for patients navigating the complexities of cancer and its treatments. Cardio-oncology holds particular significance for hematological malignancies. The recently published guidelines on cardio-oncology of the European Society of Cardiology (ESC) conjointly with the European Hematology Association focus on the CV effects of cancer treatments with specific prevention and surveillance strategies.[4] Many patients diagnosed with these cancers are relatively young and, by virtue of

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advances in treatment, currently have a high life expectancy after cancer therapy and remission or with long-term use of oral medications such as tyrosine kinase inhibitors (TKIs). For these younger survivors, the long-term cardiac implications of hematological treatments can be profound, potentially impacting their outcome and quality of life for decades.[5] In this state-of-the-art review, we give an overview of the developing field of cardio-oncology with an emphasis on hematological malignancies and hemostaseological considerations in this patient collective (►Fig. 1, central illustration). It is important to point out that while this review focuses on cardio-oncology in hematology, most of the recommendations and principles outlined also apply to patients with solid tumors.

Reverse Cardio-Oncology

Cancer and heart disease share multiple common risk factors, such as lifestyle-associated diet, smoking, obesity, metabolic syndrome, and diabetes mellitus type II (DM II). Translational research has shown an important bidirectional relationship between heart failure (HF) and cancer development, e.g., due to hypoxia, or inflammatory mechanisms.[6–8] Clonal hematopoiesis of indeterminate potential (CHIP) is the clonal expansion of mutated hematopoietic stem cells without evidence of hematological malignancy. CHIP has been identified as an independent risk factor for the development and progression of atherosclerotic disease, HF, and adverse outcomes after transcatheter aortic valve repair.[9–12] Earlier definitions of CHIP used a threshold variant allele frequency (VAF) of ≥2%, corresponding to a heterozygous population of ≥4% mutated circulating blood leucocytes. However, recent advances in deep-sequencing techniques have shown that there is a dose–response relationship between the clone size and the increased CVD risk, with a significantly increased risk being observed at VAF as low as 0.73%.[13] Several mechanistic studies have pointed toward increased inflammation as the main mechanism connecting CHIP and CVD.[14–17] In the future, screening for CHIP and high-risk mutations might be used in CV risk stratification and treatment.

General Principles in Cardio-Oncology

A general principle of cardio-oncology is that the development of cancer treatment-related cardiovascular toxicity (CTR-CVT) hinges on the patients' baseline risk, which shifts with ongoing cardiotoxic therapies.[4] To account for this, risk assessment instruments are employed to categorize cancer patients into distinct CV risk categories—low, moderate, high, and very high. This stratification is then used to create an appropriate screening and surveillance regimen to minimize interruptions of cancer therapies while also minimizing the risk of acute or chronic CV toxicity.

The ESC cardio-oncology guidelines recommend a thorough baseline CV risk assessment including an electrocardiogram (ECG) in all patients (Class I, Level B) (►Table 1). The strength of the recommendation for the inclusion of transthoracic echocardiography (TTE), troponin T, and NT-proBNP (N-terminal pro B-type natriuretic peptide) varies based on the cardiotoxic potential of the planned cancer therapy and the baseline CV risk of the patient.[4]

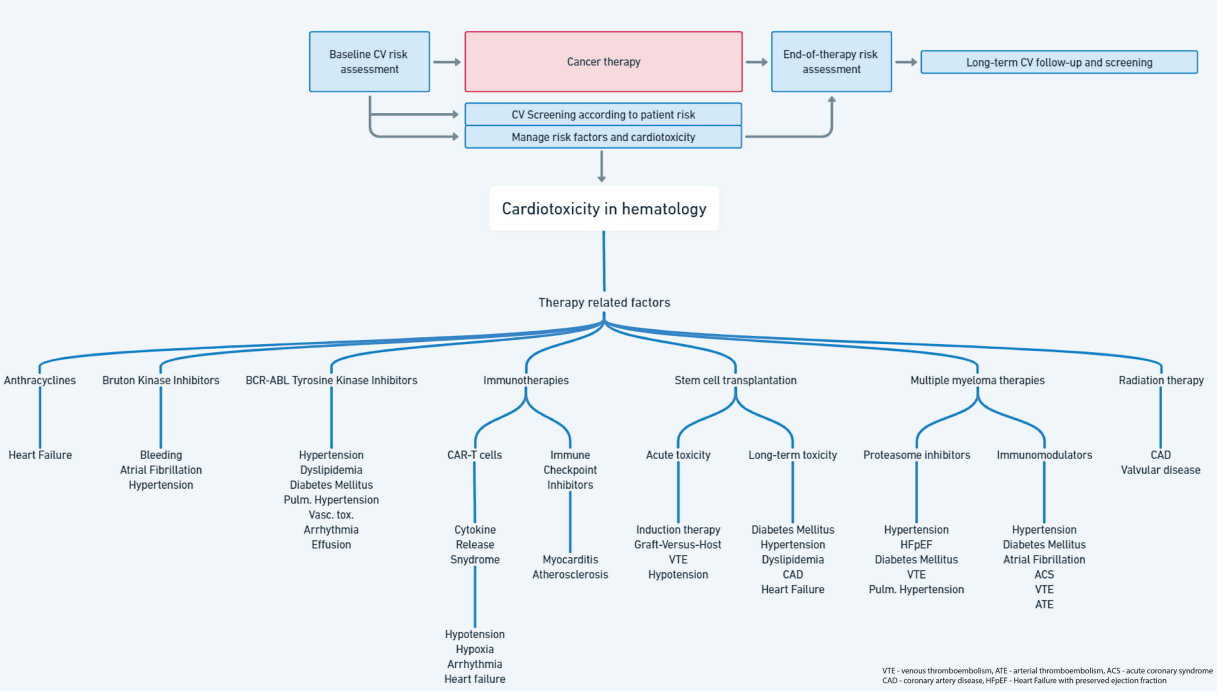

Fig. 1 Central Illustration. Cardio-oncology workflow and overview of cardiotoxicity in hematology.

Table 1 Baseline CV risk assessment checklist

History	CV history • Previous CV disease
	Oncological history • Previous cardiotoxic therapies
	CV risk factors • Smoking, exercise, family history, etc.
Examination	Physical examination
	Blood pressure
	ECG
	TTE Left ventricle: LVEF (%), GLS (%), EDV, ESV Right ventricle: RVEF, TAPSE, sPAP Valvular function
Blood tests	Lipid profile (cholesterol, LDL, HDL, Lp(a))
	Fasting glucose, HbA1c
	Troponin T
	NT-proBNP or BNP

Abbreviations: CV, cardiovascular; EDV, end-diastolic volume; ESV, end-systolic volume; GLS, global longitudinal strain; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; TTE, transthoracic echocardiography.

Risk Stratification

Risk stratification tools are available in the ESC guidelines and in the ESC pocket guideline app.[4,18] The most evidence-based approach to risk stratification involves not only the CV risk profile of the patient being assessed but also the cardiotoxic potential of the planned cancer therapy.

However, in simplified terms, patients with a previous history of significant CVD such as prior myocardial infarction (MI), significant coronary artery disease (CAD), arterial peripheral or cerebral vascular disease, or preexistent HF usually already qualify as high to very high-risk patients, regardless of the planned cancer therapy.

Patients without prior manifest CVD but a combination of classic cardiac risk factors such as obesity, DM II, hypertension, dyslipidemia, kidney disease, old age (>65 years), and/or significant smoking history should generally be considered to be at moderate risk (2–4 risk factors) or high risk (≥5 risk factors).

Primary Prevention

In patients with a high to very high baseline CV risk and a planned cancer therapy with the potential to cause HF, the ESC guidelines recommend considering preemptive initiation of Beta-blockers and ACE-inhibitors (ACEi)/angiotensin-receptor blockers (ARBs; Class IIa, Level C). Therapy with statins should also be considered for cancer patients at high or very high baseline CV risk (Class IIa, Level B). Statins have been associated with improved overall mortality and even cancer recurrence in cancer patients and in cancer survivors.[19–23] In lymphoma patients undergoing anthracycline-based chemotherapy, randomized trial data suggest a reduction in the incidence of cardiac dysfunction with statin use.[24] Blood pressure should be controlled according to current guidelines where a blood pressure <130/90 mmHg is generally considered as a treatment target, and ACEi/ARB ± dihydropyridine calcium-channel-blockers are used as first-line treatment.[4,25] The cardio-oncology guidelines also define treatment thresholds for hypertension during cancer therapies. A blood pressure of >160 mmHg systolic should always be treated, even in patients with <1 year life expectancy.[4] Diltiazem and verapamil are not recommended for hypertension treatment in cancer patients due to their potential drug–drug interactions. Hypertension can be induced as a class effect, especially by vascular endothelial growth factor- and tyrosine kinase-inhibitors and should be closely controlled during therapy.

Secondary Prevention

In patients with pre-existing CVD, the guidelines recommend management according to the latest respective clinical practice guidelines before, during, and after cancer treatment (Class I, Level C).

The simplest but most impactful application of cardio-oncology in daily practice is the adequate treatment of all modifiable CV risk factors in cancer patients and an appreciation for the fact that cancer and its therapies can amplify the cumulative impact of these risk factors. Patients should be advised of this interaction and the long-term benefits of lifestyle modification and risk factor management, such as therapy adherence, weight loss,[26] exercise,[27,28] and smoking cessation.[29,30] The general approach to primary and secondary prevention in cardio-oncology is summarized in ►**Fig. 2**.

Cardiotoxicity of Commonly Used Chemotherapies in Hematology

Anthracyclines such as doxorubicin, epirubicin, daunorubicin, mitoxantrone, or idarubicin are considered the prototypical representatives of cardiotoxic chemotherapies. Anthracyclines cause dose-dependent, potentially irreversible left ventricular dysfunction and HF, termed cancer therapy-related cardiac dysfunction (CTRCD) in the guidelines.

Infusions of dexrazoxane should be considered in patients receiving high cumulative doses (>300 mg/m^2) of anthracyclines or in those with high baseline CTRCD risk, such as patients with pre-existing HF or impaired left ventricular ejection fraction (LVEF) in whom anthracycline therapy is considered essential (Class IIb, Level B).[4] The use of pegylated or liposomal doxorubicin or daunorubicin has also been associated with lower cardiotoxicity and should be considered in patients with high baseline CV risk (Class IIb, Level B). In hematological malignancies, most data exist regarding comparisons of R-CHOP versus R-COMP in lymphoma, mainly DLBCL (diffuse large B cell lymphoma).[31–36] In patients at high baseline CV risk, such as older patients, pre-existing CVD or previous high doses of anthracyclines, liposomal anthracyclines have shown similar efficacy with reduced cardiotoxicity, making them a valuable therapeutic option

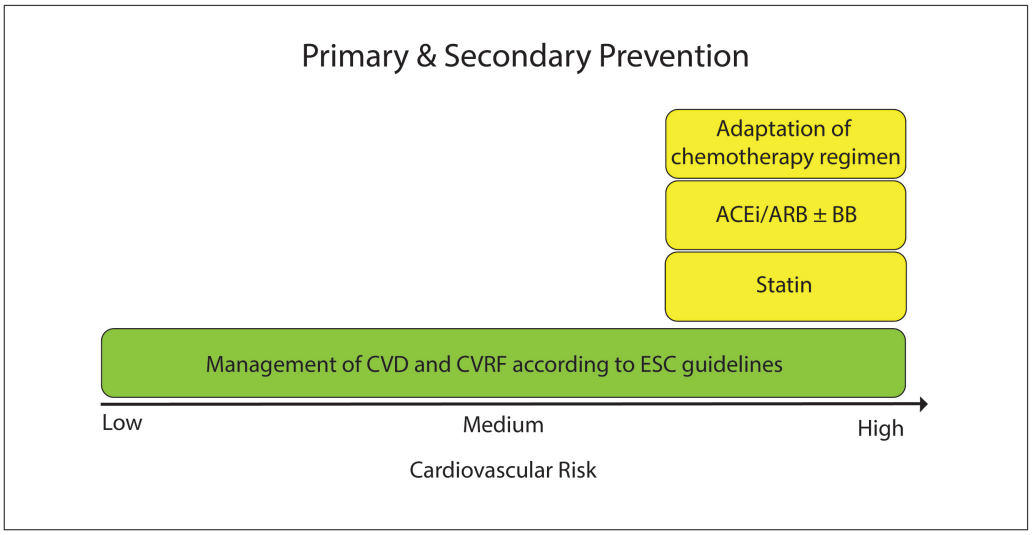

Fig. 2 General approach to primary and secondary prevention in cardio-oncology.

in these patients.[31–39] A translational study of our group demonstrated less cardiotoxicity of liposomal doxorubicin in an experimental setting.[40]

Importantly, patients with high baseline CV risk about to receive anthracyclines should be considered for initiation of beta-blockers and ACEi/ARB (Class IIa, Level B).[4]

Baseline TTE and natriuretic peptide measurement is recommended in all patients receiving anthracyclines. In high to very high-risk patients, TTE should be repeated every 2 cycles, then repeated 3 and 12 months after the end of chemotherapy (Class I, Level C).[4] Natriuretic peptides should be measured before every cycle in these patients (Class I, Level B).

If new-onset symptomatic left ventricular dysfunction is detected during anthracycline therapy, initiation of HF therapy with beta-blockers, ACEi/ARB, MRA, and SGLT2i is recommended (Class I, Level B). In severe cases of HF requiring hospitalization, anthracycline therapy should be discontinued (Class I, Level C). Importantly, in moderate to mild cases, a multidisciplinary team (MDT) should evaluate if the anthracycline therapy can be continued and if dexrazoxane or liposomal doxorubicin formulations should be considered (Class IIb, Level C). In mild asymptomatic cases of left ventricular dysfunction, defined as LVEF >50% but relative decline of GLS (global longitudinal strain) by >15% from baseline or rise in cardiac biomarkers, the therapy can be continued, but cardioprotective treatment with ACEi/ARB and beta-blockers should be considered (Class IIa, Level B). In cases where only an asymptomatic increase in natriuretic peptides is seen without any changes in TTE, the guidelines give a weak recommendation for cardioprotective therapy with ACEi/ARB and/or beta-blocker (Class IIb, Level C). In moderate to severe cases of asymptomatic CTRCD defined as a reduction of LVEF >10% compared to baseline or total LVEF <40%, the anthracycline therapy should be interrupted and full HF therapy should be initiated before the continuation of the therapy.

Cyclophosphamide and ifosfamide, alkylating agents frequently used in both hematological and solid malignancies, have been associated with rare cases of cardiomyopathy. Especially high doses (>140 mg/kg) of cyclophosphamide have been associated with the development of HF within days of administration.[41] Some evidence also links alkylating agents, primarily cyclophosphamide and mitomycin C, to the development of peripheral veno-occlusive disease, leading to pulmonary hypertension (PH).[42] Other alkylating agents such as chlorambucil, melphalan, bendamustine, busulfan, carmustine, and lomustine have not specifically been associated with cardiotoxicity. Although the guidelines give no specific recommendations for monitoring during the administration of alkylating agents, based on the previously outlined principles, high-risk patients should receive adequate screening with cardiac biomarkers and a high index of suspicion should be maintained when symptoms of HF occur.

Cardiotoxicity of Targeted Therapies in Hematology

Bruton Kinase Inhibitors

Ibrutinib is a Bruton kinase inhibitors (BTKi) used in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma, marginal zone lymphoma, Waldenström macroglobulinemia, and chronic graft-versus-host disease (GVHD).

Common CV side effects importantly include arrhythmias such as AF, and ventricular tachycardia without previous QT prolongation, but also hypertension and HF. Additionally, BTKi carries a significantly increased risk of bleeding due to platelet inhibition, causing interference with oral anticoagulation when indicated in atrial fibrillation (AF) or thromboembolism.[43] Recently, the second-generation BTKi acalabrutinib has been shown to be noninferior to ibrutinib in terms of progression-free survival (PFS) with a lower rate of symptomatic CVD.[44] However, in older patients and patients with pre-existing CVD, the rates of AF and CV events were comparable between both groups. Acalabrutinib also carries a significantly increased bleeding risk compared to other chemotherapies.[45,46] In a head-to-head comparison of

acalabrutinib with ibrutinib, bleeding events were reported significantly less frequently with acalabrutinib (38% vs. 51%, $p < 0.05$), but the rate of major bleeding events (defined as any hemorrhagic event that was serious, grade ≥3 in severity, or that was a central nervous system hemorrhage of any severity grade) was identical between groups (5% in both).[44] Another second-generation BTKi, zanubrutinib, has shown similar results to acalabrutinib in terms of PFS in CLL/SLL when tested against ibrutinib.[47] No clinical trials directly comparing acalabrutinib and zanubrutinib exist. In an unanchored, matching adjusted, indirect comparison, the rate of adverse events was broadly comparable between acalabrutinib and zanubrutinib.[48]

Patients at high to very high baseline risk for cardiotoxicity during BTKi therapy are more often male, aged ≥65 years, have a previous history of hypertension, DM II, atrial fibrillation (AF), HF, cardiomyopathy, or severe valvular heart disease.[4]

The ESC guidelines currently recommend opportunistic blood pressure measurements and AF screening even via simple pulse measurements or ECG during routine clinical visits and baseline TTE in high-risk patients about to receive BTKi (Class I).

Ibrutinib should be discontinued for 3 to 7 days before interventions with a high bleeding risk and should not be given concurrently with dual antiplatelet therapy (DAPT).[4] As for the second-generation BTKi, there are not enough data available to give different recommendations currently. However, it is plausible and appears likely that even though second-generation BTKis have a lower risk of minor bleeding events than first-generation BTKi, a combination with DAPT could potentially lead to an increased risk of major bleeding complications as their mechanism of platelet inhibition is distinct from aspirin and P2Y12 inhibitors.[49]

Overall, a high incidence of CV toxicities is observed with BTKis in real life, with a 10-fold increase in the incidence of AF with ibrutinib exposure and risk of hypertension increased two- to threefold.[50–52] Dose reduction, changing to a newer generation BTKi, and initiation of cardiac therapy should be discussed in a multidisciplinary care team, which usually enables an optimal overall prognostic treatment possibility for these patients.

TKIs Targeting BCR-ABL

TKIs targeting BCR-ABL include imatinib (first generation) bosutinib, dasatinib, nilotinib (second generation), and ponatinib (third generation). The CV side effects of drugs in this class are unique to each substance.

Dasatinib is thought to carry the highest risk of PH with prevalence reaching above 10%.[53] It also carries a significant risk of pericardial/pleural effusions, although ponatinib in the third generation also carries this risk.[4]

Importantly, all BCR-ABL TKIs in the second generation carry a risk of QTc prolongation, although this risk is most pronounced with nilotinib. Therefore, regular ECG monitoring is recommended during treatment.[4]

All BCR-ABL TKIs after the first generation carry a significant risk of hypertension, with ponatinib reaching a prevalence beyond 10%. Nilotinib and ponatinib carry a significant risk of dyslipidemia and hyperglycemia, as well as the highest risk of vascular complications such as MI, stroke, and peripheral artery disease. In a study of ponatinib, the cumulative rates of vascular events at a median follow-up of 15 months were 7.1% for cardiac events, 3.6% for cerebrovascular events, and 4.9% for peripheral-artery vascular events.[54–56]

The risk of CV toxicity is highest in patients with preexisting DM II (relative risk 2.5), advanced age (>65 years) (relative risk 1.8), hypertension (relative risk 3.2), and preexisting CAD (relative risk 2.6).[4,55,57,58]

Therefore, the current guidelines recommend a baseline CV risk assessment for all patients about to receive BCR-ABL TKIs.[4] Patients receiving nilotinib or ponatinib should receive a CV risk assessment (physical examination, blood pressure, ECG, lipid profile including total cholesterol and LDL, HbA1c) every 3 months for the first year and every 6 to 12 months thereafter (Class I, Level C).[4] In patients receiving nilotinib, QTc measurements should be done at baseline and 2 and 4 weeks, then 2 weeks after every dose increase (Class IIa, Level C).

Chimeric Antigen Receptor T Cells and Bispecific T-Cell Engager Therapy

Chimeric antigen receptor T (CAR-T) cells and bispecific T-cell engager (BiTE) therapies targeting CD19 are currently approved for the treatment of some lymphoid malignancies like ALL and B-cell lymphoma. They are also occasionally used in multiple myeloma (MM). The principle in both therapies is similar, namely the targeting of tumor-specific antigens by cytotoxic T lymphocytes, causing tumor-cell apoptosis. Most of the evidence regarding cardiotoxicity is available for CAR-T cell therapy.[59]

The majority of potentially serious cardiotoxic effects of CAR-T cell and BiTE therapy occur secondary to cytokine release syndrome (CRS), which develops in response to the widespread release of inflammatory cytokines and chemokines due to immune activation. CRS is not specific to CAR-T cell and BiTE therapy as it can also occur in other settings, such as rituximab (CD 20 targeted) therapy. CRS is graded according to the American Society for Transplantation and Cellular Therapy (ASTCT), where grade 2 is hypotension without vasopressor support and hypoxia with only low-flow O_2 nasal cannula support. Requiring at least one vasopressor and/or high-flow oxygen support is grade 3 and above.[60] CRS is a very frequent occurrence in CAR-T cell therapy with an incidence of as much as >90%.[61] Grade ≥3 CRS is less common though still usually above 10%.[61,62] In BiTE therapy, the rate of CRS of any grade has ranged from 0 to 20%,[63–66] while grade ≥3 CRS occurs in between 5 and 9% of patients. Thus far, there is a lack of data on the incidence of cardiotoxicity in BiTE therapy and no distinct recommendations for the cardio-oncological evaluation and management of these patients exist.[59] We argue that in this regard, the management should be approached similarly to CAR-T cell therapy.

The incidence of cardiac events in patients receiving CAR-T cells varies between studies but is generally between 10 and 20% and occurs mainly in CRS grade ≥2 with elevated

cardiac troponin and interleukin-6.[67–73] The most frequently observed CV events are profound hypotension requiring vasopressor support, arrhythmias including AF and ventricular tachycardias, as well as left ventricular dysfunction, decompensated HF, and CV death.[67–73]

Regarding risk stratification before CAR-T cell therapy, patients with pre-existing CVD or previous CRS of ASTCT grade ≥2 are considered to have a high to very high risk of cardiotoxicity.[4] CV complications may represent around 20% of reported adverse events.

Current recommendations for the management of high-risk patients with suspected grade ≥2 CRS secondary to CAR-T cell therapy is early transfer to an intensive care unit (grade 3) due to the significant risk of hypotensive shock and lethal arrhythmias, as well as the early administration of tocilizumab and if necessary, dexamethasone.[71] Earlier administration of tocilizumab was associated with better CV outcomes.[68] Currently, no data on the long-term CV effects of CAR-T cell therapy and BiTE therapy exist.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) are currently only used in few hematological malignancies, such as refractory Hodgkin's lymphoma and primary mediastinal B-cell lymphoma.[74] Due to their ever-expanding use in solid tumors, there is mounting evidence of their potential cardiotoxic effects in real life.

While ICIs are generally well-tolerated, their disinhibition of the patients' immune system can cause a large variety of immune-related adverse events (irAEs), which are then classified after the common terminology criteria for adverse events. Grade IV irAEs are life-threatening, while grade V is death. The incidence of grade V irAEs in the use of ICIs lies between 0.3 and 1.3%.[75]

The absolute incidence of myocarditis under ICI therapy is 0.27 to 1.14% in various studies, but the mortality rate of up to 40 to 50% is the highest among the irAEs.[76–79] Among the most lethal complications of ICI myocarditis are lethal arrhythmias such as complete heart block. A 2021 pharmacovigilance study also points toward a higher incidence of myocarditis of up to 5.16%.[80] Other irAEs frequently occur at the same time, namely myositis (25%) and myasthenia gravis (~10%).[75,77,81,82] Previous studies have shown that a median of >70% of myocarditis cases occur within the first 30 days of initiation of therapy.[83]

In addition to the rare risk of life-threatening fulminant myocarditis, increasing real-life data show that ICIs can promote atherosclerosis and thus increase the risk of CV events over time, including acute plaque rupture with MI. A Danish registry of patients with lung carcinomas or melanomas showed a significantly increased rate of cardiac events (risk 6.6–9.7%).[84] In another study, the incidence of major CV events (MACEs; including HF, acute coronary syndrome [ACS], stroke, CV death) at a median of 13 months of follow-up was 10.3% in patients receiving ICI.[85] The MACE risk was increased in patients with history of HF or valve disease. In a single-center cohort study, a threefold increased rate of the combined endpoint of MI, coronary revascularization, and ischemic stroke was recorded within 2 years after ICI therapy.[86] In a sub-study of 40 melanoma patients, the amount of aortic plaque was measured before and after therapy.[86] The rate of plaque progression was about threefold higher. Patients who received glucocorticoids during ICI therapy or who were treated with statins showed about 50% less plaque progression. A case series looking at PET CT (positron emission tomography-computed tomography) scans of 20 patients with melanoma and ICI therapy also showed an increase in plaque FDG (Fludeoxyglucose F18) uptake after initiation of therapy.[87]

The ESC guidelines recommend baseline CV risk assessment including natriuretic peptides and troponin in all patients before receiving ICIs. TTE is strongly recommended in high-risk patients (Class I, Level B), but should be considered even in low-risk patients (Class IIb, Level C). Regardless of risk, serial ECG and troponin T measurements before the first four doses and then every three doses should be considered to detect subclinical ICI cardiotoxicity (Class IIa, Level B). High-risk patients who require long-term (>12 months) ICI treatment should receive a CV assessment every 6 to 12 months (Class I, Level C).

If there is suspicion of cardiac involvement, ECG, biomarker assessment, TTE, and cardiac MRI should be obtained. MRI may be negative especially during the first 4 days and LV function can remain preserved even in myocarditis.[88] CAD or MI should be excluded as the source of troponin elevation by coronary CT or invasive angiography.[4] Cardiology/cardio-oncology involvement should be obtained early. Continuous ECG monitoring in cardiac ICI irAE is recommended due to possible ventricular arrhythmias or cardiac arrest due to high-grade conduction or atrioventricular block.[89]

Multiple Myeloma Therapies

Many different drug classes and combinations are approved in the treatment of MM. MM patients frequently have a high baseline CV risk, which then negatively interacts with the cardiotoxic effects of MM therapies.[90] Proteasome inhibitors like Bortezomib and Carfilzomib have been associated with hypertension, HF, ACSs, arrhythmias, PH, and venous thromboembolism (VTE). Carfilzomib especially carries a high risk of HF with preserved ejection fraction.[91]

MM patients have a high risk of VTE and arterial thromboembolism (ATE), especially when treated with a combination of proteasome inhibitors and immunomodulatory drugs like lenalidomide or thalidomide. The ESC guidelines list several VTE-related risk factors in patients with MM, such as previous VTE, acute infections, central venous catheter, chronic renal disease, immobilization, general surgery, autoimmune disease, CVD, DM, cigarette smoking, or obesity.[4] The current ESC guidelines recommend prophylactic doses of low-molecular-weight heparin (LMWH) in patients with MM with VTE-related risk factors (excluding previous VTE) at least during the first 6 months of therapy (Class I, Level A). Therapeutic doses of LMWH are recommended in patients with MM with previous VTE (Class I, Level B). Aspirin should be considered as an alternative to LMWH in patients with MM with no risk factors or one VTE-related risk factor

(excluding previous VTE) at least during the first 6 months of therapy (Class IIa, Level B). Low doses of apixaban or rivaroxaban may be considered as an alternative to LMWH or aspirin in patients with MM with VTE-related risk factors (excluding previous VTE) at least during the first 6 months of therapy.[4] The ASCO clinical practice guidelines recommend thromboprophylaxis with aspirin or low-dose LMWH for lower risk patients and full-dose LMWH for high-risk patients, at least during the first 6 months of therapy.[92]

In terms of surveillance, a CV baseline risk assessment including TTE and natriuretic peptides is recommended in all patients (Class I, Level C) in the ESC guidelines.[4] Measurement of blood pressure is recommended at every clinical visit due to the high incidence of hypertension. Otherwise, based on individual risk, a visit with ECG, complete blood tests (including natriuretic peptides and troponin), and TTE every 3 to 6 months should be considered.

Radiation Therapy

Radiation exposure to the heart, commonly quantified as mean heart dose (MDH) has a dose-dependent relationship with the development of long-term complications such as atherosclerosis, valvular disease, and pericardial disease. Especially early onset of CAD has been reported as long-term effects in lymphoma and breast cancer patients receiving radiation close to the heart.[30,93] The risk of long-term complications is compounded by additional cardiac risk factors, e.g., smoking, hyperlipidemia, hypertension, and DM II. For cancer survivors, annual CV risk assessment including ECG and biomarkers is recommended (Class I, level B) after radiation therapy. At 5 years, TTE should be performed. A noninvasive screening for CAD (e.g., stress test, coronary CT) is recommended at 5 years especially after a MDH >15 Gy. Chemotherapy regimens such as high anthracycline doses add to an increased high late risk in cancer survivors.[4]

Hematopoietic Stem Cell Transplantation

The acute and long-term CV toxicities following hematopoietic stem cell transplantation (HSCT) are increasingly recognized as an important factor in the prognosis of stem cell recipients.[29,94]

The acute CV toxicities of HSCT range from arrhythmias like AF to hypo- and hypertension to VTE. Acute GVHD is associated with thrombosis and inflammatory myocardial damage (myocarditis, HF, conduction abnormalities, arrhythmias, and pericardial effusions).

Long-term toxicities include DM II, dyslipidemia, metabolic syndrome, hypertension, HF, CAD, conduction disorders, and pericardial effusion. The risk for the development of CAD scales with the presence and control of CV risk factors at the time of HSCT, as well as radiation exposure.[94,95]

High baseline CV risk characteristics for stem cell transplantation are allogenic HSCT, pre-existing CVD, multiple CV risk factors, cancer treatment history (mediastinal or mantle field radiation, alkylating agents, >250 mg/m^2 doxorubicin or equivalent), conditioning schemes including total body irradiation and/or alkylating agents and GVHD. If some or all of these factors are present, the patient should be considered to be at high risk of acute and long-term CV toxicities secondary to HSCT.

The current guidelines recommend a baseline CV risk assessment including TTE and natriuretic peptides in all patients prior to HSCT. Follow-up visits with physical examination, blood pressure measurement, and ECG should be scheduled every 3 months, with TTE and natriuretic peptides being recommended only in high-risk patients or in low-risk patients presenting with new-onset cardiac symptoms.

Anticoagulation Management in Cardio-Oncology

Anticoagulation presents unique challenges in cancer patients. Both cancer and its treatment can predispose patients to thrombotic events, while at the same time increasing the risk of bleeding due to various factors. The ESC guidelines offer a structured approach based on the TBIP acronym:

- *T*hromboembolic risk.
- *B*leeding risk.
- Drug–drug *I*nteractions.
- *P*atient preference.

Risk of VTE in Cancer Patients

Cancer increases VTE risk multiple-fold, with cancer patients accounting for 20 to 30% of all VTE cases.[96] A recent Austrian analysis based on social security data calculated that patients with cancer had a relative risk of 14.91 for VTE compared to patients without cancer.[97] A Danish registry showed a 12-month cumulative VTE incidence of 3% after cancer diagnosis, which is around 9.1 times that of the general population.[98] In patients receiving chemotherapy or targeted therapy, the 12-month cumulative incidence for VTE was 5.3%.[98] Interestingly, they also found that the 12-month incidence of VTE tripled between 1997 and 2017, likely owing to longer survival, increased CT-imaging, and earlier start of chemotherapy after diagnosis.[98] The risk for VTE peaks after cancer diagnosis, during hospitalization, chemotherapy, and with metastatic disease. An unprovoked VTE can be an early sign of cancer, with a 5% chance of cancer diagnosis within a year.[99,100] The occurrence of VTE in cancer patients is associated with poor prognosis.[101,102] In a Danish study, the mortality ratio in the first year after VTE was 4.34 and 3.44 in the following 5 years compared to cancer patients who did not develop VTE.[103]

Both LMWH and direct oral anticoagulants (DOACs) (apixaban, edoxaban, rivaroxaban)[104,105] are suitable for the treatment and recurrence prevention of deep vein thrombosis (DVT) ± pulmonary embolism (PE) in patients with cancer. DOACs are recommended unless the following risk factors are present:

- Unoperated gastrointestinal (GI) or genitourinary malignancies.
- History of recent bleeding or within 7 days of major surgery.

- Significant thrombocytopenia (platelet count < 50,000/μL).
- Severe renal dysfunction (creatinine clearance [CrCl < 15 mL/min]).
- GI comorbidities.
- Drug–drug interactions.[106,107]

In patients with these risk factors, anticoagulation therapy should be discussed and individualized by a MDT. LMWH is generally a safe and effective treatment for cancer-related thrombosis, especially in a hospital setting or in the initial stages after the diagnosis of thrombosis. For cancer patients with platelet counts 25,000 to 50,000/μL, the ESC guidelines advise consideration of half-dose LMWH after MDT discussion (Class IIb, Level C).[4]

The minimal treatment duration after DVT ± PE is 6 months and extended anticoagulation is recommended in the presence of active malignancy, metastatic disease, or chemotherapy.[4,92] Cancer patients have a high risk of DVT ± PE recurrence, especially if anticoagulation is discontinued after 3 months.[108]

Primary Prophylaxis of VTE

Considering the negative impact of VTE on the overall prognosis in cancer patients, primary prophylaxis of such events is a major concern that is frequently overlooked in daily practice.[109–111] In most hospitalized patients, primary prophylaxis with low-dose LMWH is recommended (Class I, Level B). After major cancer surgery, extended prophylaxis with low-dose LMWH is recommended for 4 weeks following surgery in patients with low bleeding risk and high VTE risk.[112,113] The most recent update of the ASCO VTE guidelines also include a weak recommendation for prophylactic-dose apixaban or rivaroxaban for 4 weeks after an initial period of LMWH, after two randomized controlled trials have shown the safety and feasibility of this strategy.[114,115]

For primary prevention in ambulatory patients, VTE risk should be assessed using scores such as the one developed by Khorana et al.[116] In the AVERT trial, the use of apixaban 2.5 mg b.d. was effective in reducing VTE in intermediate- to high-risk ambulatory patients (4.2% vs. 10.2% VTE in apixaban vs. placebo) starting chemotherapy at the cost of increased bleeding complications (3.5% vs. 1.8%).[117] In the CASSINI trial, the use of 10 mg rivaroxaban resulted in a non-significant reduction in the incidence of VTE in ambulatory high-risk patients.[118] Apixaban and rivaroxaban, along with LMWH, should be considered for the primary prevention of VTE in high-risk (Khorana score ≥ 2) patients without significant contraindications according to the ESC guidelines (Class IIb, Level B) and the ASCO clinical practice guidelines.[92]

In terms of drug interactions, the rate of major bleeding events was highest when DOACs were used concurrently with BTKi (10%), vascular endothelial growth factor TKIs (7%), and epidermal growth factor receptor/anaplastic lymphoma kinase inhibitors (2%).[119,120] In general, strong modulators of CYP3A4 or P-glycoprotein (P-gp) are likely to cause significant drug–drug interactions with DOACs.[107]

Risk of ATE in Cancer Patients

Cancer patients are at a vastly increased risk of ATE compared to patients without cancer. Population data show an increased relative risk for ATE of 6.88 in cancer patients compared to patients without cancer.[97]

In one study, the risk of ATE increased 150 days before diagnosis and peaked in the 30 days before diagnosis (0.62% vs. 0.11%).[121] The 6-month cumulative incidence of ATEs (4.7% vs. 2.2%), MI (2.0% vs. 0.7%), and ischemic stroke (3.0% vs. 1.6%) was higher in cancer patients than matched controls without cancer.[122] In a cohort of acute myeloid leukemia patients, 2.9% developed ATE within a median of 3 months of diagnosis with a staggering mortality of 50%.[123] In another recent analysis, the 6-month cumulative incidence of ATE was 1.5% vs. 0.76% in cancer patients versus matched controls.[124]

AF is associated with cancer, with cancer patients exhibiting an up to 10-fold increased relative risk ratio of AF compared to patients without cancer.[125] The same study found a prevalence of 9.77% AF in cancer patients. The strongest association of AF and cancer was found in younger patients and patients with hematological malignancies. In cancer patients with AF, the commonly used CHA2DS2-VASc score underestimates the ATE risk. Because of this, the ESC guidelines recommend considering long-term anticoagulation even in men with score 0 (Class IIb) and score 1 (Class IIa) and in women with a score of 1 (Class IIb) and score 2 (Class IIa). This recommendation has been validated by a recent analysis showing a 2.13% 12-month cumulative incidence of ATE in cancer patients with AF, with the highest risk in male patients with a score of 1 and female patients with a score of 2.[126] In cancer patients with AF and high bleeding risk, a recent study has shown the feasibility of left atrial appendage occlusion.[127]

The efficacy of anticoagulation in preventing ATE in cancer patients without AF is poorly understood. A recent meta-analysis with over 10,000 patients found no reduction of ATE events in patients taking LMWH, DOACs, or warfarin.[128] The role of antiplatelet therapy in this collective is also undetermined. Data from the RIETE registry showed an ATE rate of 1.1% over a median of 7.3 months after VTE, where intriguingly, only a minority of cases (6.3%) occurred when anticoagulation and antiplatelet therapy were given concurrently.[129,130] After 30 days of follow-up, 59% of patients with ATE had died. However, the overall main cause of death in this post-VTE cohort was bleeding (6.1% bleeding, 41% of which died), rather than recurrence of VTE or new-onset ATE.[129] At present, no recommendations for the combination of antiplatelet and anticoagulation therapy exist in cancer patients.

End of Therapy CV Assessment and Long-Term Follow-Up

At the end of cancer therapy, a CV risk assessment should be repeated. In patients treated with long-term oral drugs, the end-of-cancer therapy CV risk assessment should be done after the induction and consolidation therapies are finished.

It has been well established that early detection and treatment of CTR-CVT after for example anthracycline therapy is associated with better response to therapy and that a delay in detection and treatment >6 months resulted in irreversible LVEF decline.[131]

Cancer survivors at high risk of early (<5 years after treatment) CV complications generally fulfill some or all of the following criteria: (1) ≥ high baseline CV risk, (2) cardiotoxic cancer therapy with high risk of long-term complications (doxorubicin >250 mg/m^2, RT >15 Gy MHD, doxorubicin >100 mg/m^2 + RT 5–15 Gy MHD, high-risk HSCT patients), (3) moderate or severe CTR-CVT during cancer treatment, and/or (4) newly abnormal cardiac imaging, biomarkers or symptoms after the end of treatment. Patients with high doses of radiation or radiation and anthracyclines and poorly controlled CV risk factors are at high risk for late complications (>30 years after treatment).

In asymptomatic high-risk patients, TTE and serum biomarkers are recommended at 3 and 12 months after end-of-therapy (Class I, Level B). In asymptomatic moderate risk, TTE and serum biomarkers should be considered 12 months after end-of-therapy (Class IIb, Level B). All patients in whom CV therapies for any CTR-CVT were initiated during cancer therapy should receive a CV assessment including ECG, TTE, and serum biomarkers at 3, 6, and 12 months after end of therapy. In patients having developed CTRCD, HF medication should be continued indefinitely in all ≥ severe cases. In mild to moderate cases of CTRCD with full recovery of LVEF under HF therapy, weaning can be considered in low-risk patients after 12 months. In high-risk patients, HF therapy should be continued because of the high risk of recurrence of HF.

Beyond the First Year

For long-term follow-up, all patients should receive an annual CV risk assessment regardless of risk. In high-risk patients with no abnormal findings at the first 1-year assessment, a TTE starting every 5 years after therapy should be considered. For patients with high long-term atherosclerosis risk, such as after radiation exposure, noninvasive CAD screening with coronary CT and other vascular screening such as carotid ultrasound should be considered every 5 to 10 years.[132]

Conclusion and Outlook

The field of cardio-oncology is increasingly gaining momentum as the importance of CV risk and CV toxicity in cancer patients is recognized. In this review, we have given an overview of the field with a focus on hematology and hemostaseology.

Multiple scientific questions remain to be addressed, and many of the recommendations within the recent ESC cardio-oncology guidelines are only supported by a low level of evidence.[133] Cancer patients have specifically been excluded in many clinical trials, leading to large gaps in evidence. Such is the case for SGLT2 inhibitors, where only limited data exist in cancer patients. The use of statins and other therapies for hyperlipidemia and their risk to benefit ratio in patients receiving immune-checkpoint inhibitors remain to be determined. The risk stratification and screening recommended in the guidelines lack validation. There are little data on the long-term effects of T-cell therapies such as CAR-T and BiTE.[59] Regarding the prevention of VTE and ATE, more trials are needed to clarify optimal prevention and recurrence strategies. Upcoming studies on factor XI inhibitors in cancer patients are eagerly awaited as well.[134]

The field is rapidly evolving and close scientific and clinical collaboration with oncology, hematology, and cardiology specialists in the field of cardio-oncology will further optimize acute and long-term outcomes of cancer patients.

Conflict of Interest

Both authors received a grant from Boehringer Ingelheim for SGLT2i in cardio-oncology patients.

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