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Management of cancer patients at high and very-high risk of cardiotoxicity: Main questions and answers

Daniela Di Lisi [a,*], Christian Cadeddu Dessalvi [b], Concetta Zito [c], Cristina Madaudo [a], Roberta Manganaro [c], Valentina Mercurio [d,e,f], Martino Deidda [g], Ciro Santoro [h], Claudia Penna [i], Ines Paola Monte [j], Paolo Spallarossa [g], Carlo Gabriele Tocchetti [d,e,f,k], Giuseppina Novo [a]

[a] Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Division of Cardiology, University Hospital Paolo Giaccone, Palermo, Italy.
[b] Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy
[c] Department of Clinical and Experimental Medicine - Cardiology Unit, University of Messina, Messina, Italy
[d] Department of Translational Medical Sciences, Federico II University, Naples, Italy
[e] Interdepartmental Center of Clinical and Translational Sciences (CIRCET), Federico II University, Naples, Italy
[f] Interdepartmental Hypertension Research Center (CIRIAPA), Federico II University, Naples, Italy
[g] Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, Italy-IRCCS Italian Cardiovascular Network & Department of Internal Medicine, University of Genova, 16121 Genova, Italy.
[h] Department of Advanced Biomedical Sciences, Federico II University, 80131 Naples, Italy
[i] Department of Clinical and Biological Sciences of Turin University, Orbassano, Turin, I-10043, Italy
[j] Department of General Surgery and Medical-Surgery Specialities- Cardiology, University of Catania, Catania, Italy
[k] Center for Basic and Clinical Immunology Research (CISI), Federico II University, Naples, Italy

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ABSTRACT

In recent years, important advances have been made in the field of Cardio-Oncology. The 2022 ESC Guidelines on Cardio-Oncology proposed a baseline cardiovascular risk stratification for cancer patients and preventive strategies in patients at high and very-high risk of cardiotoxicity.

Cardiovascular toxic effects of anti-cancer drugs are being extensively studied; surveillance programs have been proposed, based on the baseline cardiovascular risk.

On the other hand, there is little data on Cardio-Oncological management of patients at high and very-high cardiovascular risk with previous cardiovascular diseases.

For example, little is known about management of cancer patients with heart failure with reduced ejection fraction (HFrEF), patients with a recent myocardial infarction or other cardiovascular diseases; when to resume anti-cancer drugs after a cardiovascular toxic event.

Collaboration between Cardiologists and Oncologists and multidisciplinary team evaluations are certainly essential to decide the best therapeutic strategy for cancer patients, to treat cancer while saving the heart.

Therefore, in the present review, we attempt to provide a useful guide to clinicians in treating patients with high and very-high risk of cardiotoxicity by enucleating main questions and answering them based on the evidence available as well as expert opinion and our clinical experience.

* Corresponding author.
E-mail address: danydilis@hotmail.it (D. Di Lisi).

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Introduction

In recent years, important advances have been made in the field of Cardio-Oncology.

It is known that anti-cancer drugs can cause cardiovascular toxic effects with several mechanisms.[1–2] For example, anthracyclines and HER2-targeted therapies predominantly cause left ventricular dysfunction and heart failure (HF).[3]

Also vascular endothelial growth factor inhibitors (VEGFi) can cause left ventricular dysfunction, arterial hypertension, venous and arterial thrombotic events, myocardial ischemia, QTc prolongation.[4–5]

Small-molecule tyrosine kinase inhibitors (TKIs) targeting BCR-ABL (especially nilotinib and ponatinib) can cause arterial hypertension, vascular toxicity (myocardial ischemia, peripheral artery diseases, accelerated atherosclerosis).[6]

Immune checkpoint inhibitors (ICI) can cause myocarditis, heart failure, vasculitis, atrio-ventricular block, supraventricular and ventricular arrhythmias, sudden death, pericarditis, pericardial effusion, ischaemic stroke and dyslipidaemia.[7]

The 2022 ESC Guidelines on Cardio-Oncology[8] and ESMO consensus recommendations[9] have defined the treatment of cardiovascular complications during the use of anti-cancer drugs. For example, during treatment with anthracyclines, the development of cancer therapy-related cardiac dysfunction (CTRCD) asymptomatic moderate or severe needs to interrupt the treatment with anthracyclines and to start HF therapy. Discussion with a multidisciplinary team is recommended before restarting anthracycline chemotherapy after left ventricular (LV) function recovery. In case of mild CTRCD, treatment needs to continue with cardiovascular monitoring. Severe symptomatic CTRCD requires the discontinuation of anthracyclines. In rare exceptions, anthracycline chemotherapy may be restarted after recovery of LV function with optimal HF therapy.

Similar recommendations exist for HER2-targeted therapy. For patients in whom HER2-targeted therapy has been interrupted, whose signs and symptoms of HF do not resolve and/or LVEF remains $<$ 40 %, resumption of HER2-targeted therapy may be considered if no alternative therapeutic option exists.[8] In advanced cancer that only responds well to trastuzumab, the risk/benefit ratio may warrant continued therapy if other options remain limited.

For patients who have interrupted HER2-targeted therapy and who have recovered from LVEF $\geq$ 40 % and are now asymptomatic, resumption of HER2-targeted therapy should be considered, supported by HF therapy.[8]

The 2022 ESC Guidelines on Cardio-Oncology recommend baseline cardiovascular risk stratification, using the new risk assessment tools proposed by the Heart Failure Association (HFA) of the European Society of Cardiology and the International Cardio-Oncology Society (ICOS).[8–10]

This score categorizes patients according to their risk of developing cardiotoxicity (low, medium, high, very-high risk) based on cancer-related risk factors (previous chemotherapy or radiotherapy to left chest or mediastinum) and patients-related risk factors (age, cardiovascular risk factors, cardiovascular diseases).[8–10]

The risk of future cardiotoxicity for each of the risk groups can be categorized as follows: low risk $<$ 2 %, medium risk 2 – 9 %, high

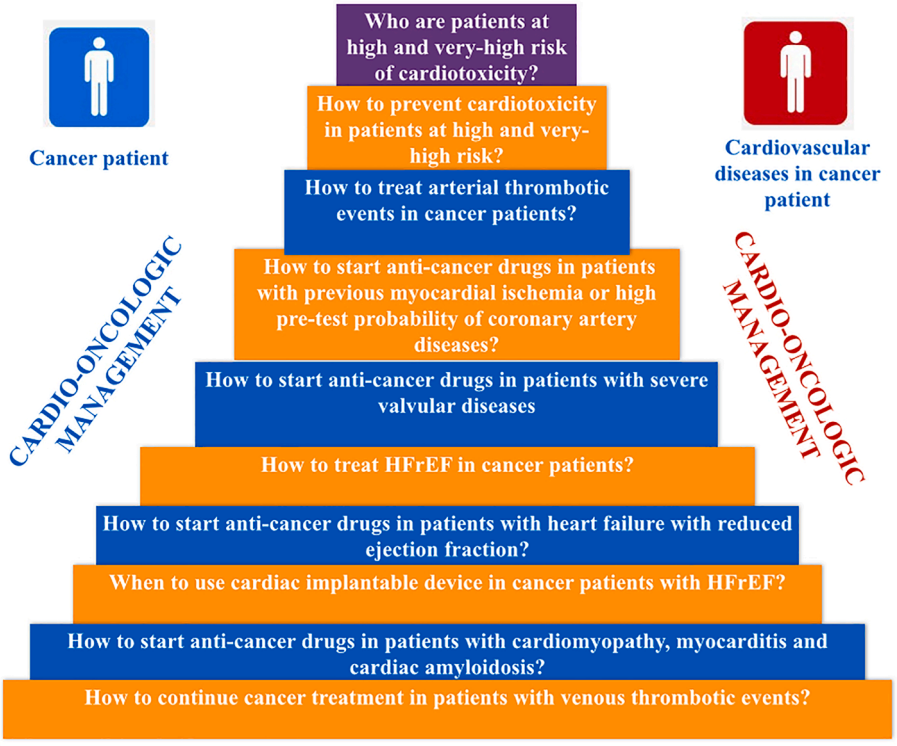

Fig. 1. Main questions in the management of high and very high risk cancer patients.

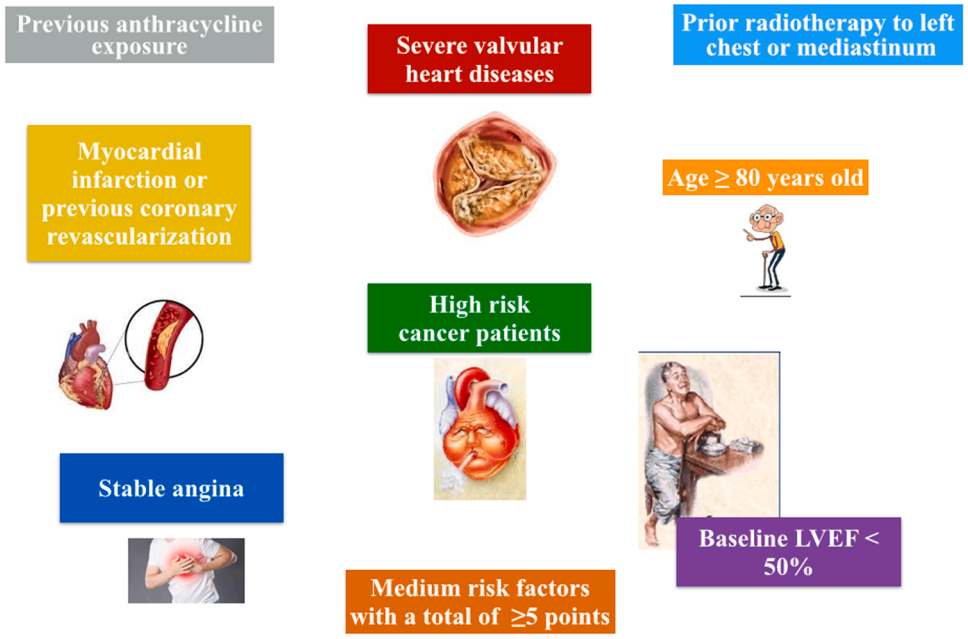

Fig. 2. Isolated high risk factors in cancer patients before anthracyclines.

risk 10 – 19 %, very-high risk ≥ 20 %.[10]

HFA/ICOS risk score has been calculated in several studies to assess its ability to predict cardiotoxicity[11–13]; surveillance programs have been planned on the basis of baseline cardiovascular risk and anti-cancer drug used.[8]

Considering high and very-high risk patients, the cancer treatment is not always easy, especially in patients with HFrEF, ischemic heart disease with reduced LVEF, patients with multiple risk factors and high pre-test probability of coronary artery disease. A multidisciplinary team and a close collaboration between the cardiologist and oncologist are certainly essential to decide the best therapeutic strategy in cancer patients, to treat cancer while saving the heart. Therefore, based on the current review, we attempt to provide a useful guide to clinicians treating patients at high and very-high risk of cardiotoxicity by enucleating main questions (Fig. 1) and answering them based on the evidence available as well as expert opinion and our clinical experience.

Who are patients at high and very-high risk of cardiotoxicity?

Patients with severe valvular heart diseases, myocardial infarction or previous coronary revascularization, stable angina, baseline LVEF < 50 % and age ≥ 80 years old are patients at high risk of cardiotoxicity, before starting anthracyclines or HER2 targeted therapy.[10] (Fig. 2). Patients with heart failure or cardiomyopathy are also patients at very-high risk.[10] (Fig. 3).

In addition, patients with several cardiovascular risk factors (sum of medium risk factors ≥ 5 points) are high-risk patients.[10] Patients at medium risk are the ones with: arterial hypertension, diabetes mellitus, chronic kidney disease, current smoker or significant smoking history, obesity (BMI >30 kg/mq), elevated baseline troponin, elevated baseline BNP or NT-pro BNP, age 65–79 years, LVEF borderline 50-54 % and previous non-anthracycline-based chemotherapy.[10]

Patients with previous anthracycline exposure and prior radiotherapy to left chest or mediastinum are considered at high risk when they have to start anthracyclines, at medium risk if they have to undergo trastuzumab (TRZ), while prior trastuzumab cardiotoxicity gives the patient a high risk of CTRCD when she has to be treated again with trastuzumab.[10]

Patients who already have arterial vascular disease, before starting VEGFi or BCR-ABL inhibitors, are patients at very-high risk. Venous thrombosis also makes a patient at high risk for cardiotoxicity, before VEGFi.

HFA/ICOS risk score should be assessed easily using the calculator proposed by the ESC and ESC cardio-oncology guidelines.[8–10]

Cardiovascular risk factors should be identified and corrected in all patients before starting anti-cancer treatment.

Optimization of the cardiovascular risk profile should be performed in all cancer patients before, during and after chemotherapy.[14]

How to prevent cardiotoxicity in patients at high and very-high risk?

Based on the results of several trials,[15–17] for primary prevention the ESC Guidelines on Cardio-Oncology recommend angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) and beta-blockers, for patients at high and very-high risk of cardiotoxicity, before starting anti-cancer drugs that may cause LV dysfunction.[8]

A treatment with statins should be considered for primary prevention in adult patients with cancer at high and very-high CV toxicity risk.[8–19]

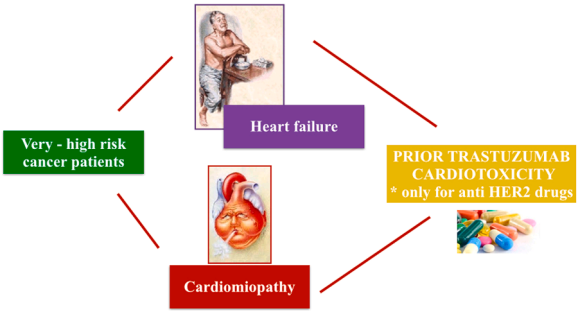

Fig. 3. Isolated very high risk factors in cancer patients before anthracyclines and HER2-targeted therapy.

The current meta-analysis of all randomized controlled trials (RCTs) conducted so far shows an overall beneficial effect of statins on the risk of anthracyclines induced cardiotoxicity and LVEF preservation.[20]

Although in a multicenter double-blinded, placebo-controlled trial, Thavendiranathan and coworkers showed that in patients at increased risk of CTRCD, primary prevention with atorvastatin during anthracycline therapy did not ameliorate early LVEF decline, LV remodeling, CTRCD, change in serum cardiac biomarkers, or CMR myocardial tissue changes, compared to placebo.[21] More powered RCTs are needed to fully investigate the impact of statins on prognosis in patients receiving anthracyclines therapy.

In patients at high and very-high risk, surveillance and monitoring program should be more intense.[10–22]

Other preventive strategies in adult patients with cancer at high and very-high CV toxicity risk, when anthracycline chemotherapy is indicated, include the use of dexrazoxane and liposomal anthracyclines.[8]

Cardioprotective action of dexrazoxane has been demonstrated in various studies: dexrazoxane stops necroptosis in cardiomyocytes after anthracycline therapy and concurrently binds with iron and reduces the formation of anthracycline-iron complexes and reactive oxygen species.[23]

The efficacy of dexrazoxane has been demonstrated in clinical trials within the pediatric population and dexrazoxane seems to be effective in cancer children. In particular, routine use of dexrazoxane in children with cancer who are at risk of anthracycline-related cardiotoxicity should be considered.[24]

Liposomal doxorubicin is less cardiotoxic than conventional doxorubicin and it should be used in patients at high and very-high CV toxicity risk.[25]

In addition, considering cardiovascular toxic effects caused by BCR-ABL tyrosine kinase inhibitors (especially arterial occlusive events), a preventive treatment with aspirin should be considered in patients aged ≥60 years treated with ponatinib.[26]

How to treat arterial thrombotic events in cancer patients?

Cancer and cardiovascular disease share many risk factors.[27] Cancer induces pro-inflammatory and prothrombotic states that favor acute coronary syndrome. Many cancer patients develop myocardial ischemia or other arterial thrombotic events during cancer treatment, especially during treatments with VEGFi, ICI, platinum compounds (cisplatin, carboplatin, oxaliplatin), antimetabolites (5-FU, capecitabine, gemcitabine, cytarabine, fludarabine), taxanes (docetaxel, paclitaxel) and vinka alcaloids (vinblastine, vincristine), BCR-ABL inhibitors.[28]

Specifically, VEGFi can cause coronary thrombosis;[29] BCR-ABL inhibitors (ponatinib and nilotinib) can cause arterial occlusive events by accelerated atherosclerosis or coronary thrombosis;[30] ICI can cause plaque rupture, vasculitis and coronary vasospasm.[31]

Other drugs can cause myocardial ischemia inducing vasospasm (for example platinum compounds, antimetabolites, taxanes).[32]

Treatment of acute arterial thrombotic events (acute coronary syndrome) in cancer patients follows the same guidelines as the general population, but greater attention is required in assessing the risk of bleeding, the presence of thrombocytopenia, frailty and the possible need for future surgery/interventions.[28]

An invasive strategy is recommended in patients with cancer presenting ST-segment elevation myocardial infarction (STEMI) or high-risk non-ST-elevation acute coronary syndrome (ACS) with expected survival ≥ 6 months, or, irrespective of the prognosis, if the patient is unstable.[8–33,34]

A conservative non-invasive strategy should be considered in ACS patients with poor cancer prognosis (expected survival < 6 months) and/ or very high bleeding risk.[8–34]

In fact, studies reported that invasive management in patients with advanced cancer or life expectancy < 6 months is not associated with mortality benefit compared to conservative approach.[34]

In addition, cancer patients have high bleeding risk and the preferred P2Y12 inhibitor for ACS patients with active cancer is clopidogrel that is not recommended in cancer patients with a platelet (PLTs) count <30 000/μL. Aspirin is not recommended in cancer patients with PLTs <10 000/μL.

Prasugrel or ticagrelor are not recommended if PLTs <50 000/μL.[34]

A temporary interruption of cancer therapy is recommended in patients in whom such treatment is suspected as a contributing cause of myocardial ischemia; alternative cancer therapy should be considered after multidisciplinary discussion.

If there are no other effective oncological therapies, the treatment with drugs that caused coronary thrombosis and myocardial ischaemia could be resumed after multidisciplinary discussion, appropriate patient education and consent.

In patients with myocardial ischemia due to vasospasm, fluoropyrimidines may be resumed, if there are no other therapeutic alternatives after exclusion of severe coronary artery diseases and prophylactic initiation of long-acting nitrates and calcium channel blockers.[35]

Treatment of peripheral artery diseases in cancer patients is similar to patients without cancer, a multidisciplinary approach regarding the decision to continue vs. interrupt culprit cancer therapy is recommended.[8–36]

How to start anti-cancer drugs in patients with previous myocardial ischemia or high pre-test probability of coronary artery diseases?

Starting anti-cancer treatment in patients with previous myocardial infarction (PCI - percutaneous coronary intervention, coronary artery bypass graft), stroke, transient ischaemic attack or peripheral vascular diseases, is not always easy. These patients are at very-high risk of cardiotoxicity, before treatment with VEGFi, BCR- ABL inhibitors, proteasome inhibitors and immunomodulatory, and at high risk of cardiotoxicity for other drugs.

A baseline cardiological evaluation is necessary, as recommended by the ESC Cardio-oncology Guidelines, in high and very-high risk patients;[8] a multidisciplinary discussion is necessary in order to personalize the choice of drugs that do not cause myocardial ischemia.

If there are no therapeutic alternatives, these drugs must be started under close monitoring, after optimization of the anti-ischaemic therapy.

In patients with residual coronary stenosis, consider performing a stress test before starting anti-cancer drugs that can cause myocardial ischaemia, if the test doesn't delay the start of anti-cancer treatment and if the prognosis is $>$ 6 months.[28]

Also, in patients with multiple cardiovascular risk factors and high pre-test probability of coronary artery disease (CAD), an imaging stress test or coronary tomography (CT) should be considered before starting treatments with anti-cancer drugs that can cause myocardial ischaemia, if the execution of this test does not delay the start of the antineoplastic treatment and if the prognosis is $\geq$ 6 months.

Myocardial revascularization before starting anti-cancer drugs should be considered in symptomatic patients with high extent of ischemia to non-invasive tests, expected survival $\geq$ 6 months, no high bleeding risk taking into account the possibility of a reduction in PLTs and the need for dual antiplatelet therapy during chemotherapy and after coronary percutaneous revascularization. There are no extensive data, multidisciplinary decisions are essential case by case.

Correction of cardiovascular risk factors and optimization of medical therapy remain essential in these patients, before starting anti-cancer drugs.

During treatment, a strict surveillance protocol is required for these patients.

In addition, to rule-out CAD, a coronary CT, stress echocardiography, myocardial scintigraphy or stress cardiac magnetic resonance may be used in cancer patients.[37]

Coronary CT value in cardio-oncology is nowadays confined to rule-out CAD in case of reduced LVEF.[33] Radiation exposure issues still represent a major limitation to coronary CT use in cancer patients, although new multidetector machines already maximally reduce the dosage.[38]

Stress echo is preferable to coronary CT for cancer patients because it is not associated with radiation exposure, it is preferable in cancer patients with good acoustic windows.[39]

Stress cardiac magnetic resonance could be used safely in cancer patients but it is time consuming and it requires specific expertise.

How to start anti-cancer drugs in patients with severe valvular diseases

In patients with cancer and pre-existing severe valvular diseases (VHD), the recommended management of VHD is according to the 2021 ESC/EACTS Guidelines, taking into consideration cancer prognosis and patient preferences.[40]

Particularly, before starting cancer therapy, a multidisciplinary discussion is required to decide the best treatment option, without delaying anti-cancer treatment. If valve treatment is the best option, a multidisciplinary discussion is recommended regarding type of valve treatment and periprocedural management of cancer treatments. If valve disease treatment is delayed, medical therapy must be optimized before and during oncological treatment.

In addition, cardiac surgery is challenging in cancer patients because of frailty, comorbidities, me- diastinal fibrosis due to prior radiotherapy, the need for urgent oncological treatment and poor wound healing while on VEGFi.[8]

Therefore, transcatheter aortic valve implantation (TAVI) should be considered in cancer patients with symptomatic severe aortic stenosis. TAVI reduces hospitalization days compared to cardiac surgery and allows to resume chemotherapy earlier.[41]

Also, in patients with symptomatic severe aortic stenosis, TAVI or surgical aortic valve replacement should be considered before high or intermediate non cardiac surgery to remove the cancer.[42]

Emerging data exist about feasibility of TAVI in cancer patients.[43]

Landes and colleagues showed that TAVI in cancer patients is associated with similar short-term but worse long-term prognosis compared to patients without cancer; mortality was largely driven by cancer.[44]

Further clinical trial and registry studies are needed to better appreciate TAVI outcomes in the cancer population.

How to treat HFrEF in cancer patients?

The treatment of heart failure with reduced LVEF (HFrEF) in cancer patients is the same as the treatment of the patient without cancer.

HF therapy should be optimized in cancer patients using the four pillars: ACEI/ARB, betablockers, mineralocorticoid receptor antagonist, dapaglifozin or empaglifozin, sacubitril/valsartan. They should be used to reduce the risk of HF hospitalization and death.[45]

While the role of ACEI/ARBs and beta-blockers has been extensively investigated in the prevention and treatment of cardiotoxicity,[15–17] emerging studies are demonstrating the efficacy of sacubitril/valsartan and sodium-glucose cotransporter 2 (SGLT2) inhibitors in the treatment and prevention of cardiotoxicity in cancer patients.

Frey and coworkers showed that sacubitril/valsartan is generally well tolerated in patients with HFrEF and history of cancer, improving LV function and biomarkers.[46]

Other studies showed effectiveness of sacubitril/valsartan in cancer patients with HFrEF and CTRCD, improving echocardiographic functional and structural parameters, N-terminal pro-B-type natriuretic peptide levels and symptomatic status.[47]

The MAINSTREAM trial is ongoing to determine the efficacy and safety of treatment with sacubitril/valsartan as a prevention of cardiotoxicity in patients with early breast cancer.[48]

Also, SGLT2 inhibitors could be used in cancer patients with HFrEF and to treat severe CTRCD.

Studies have evaluated the effectiveness of SGLT2 inhibitors in preventing cardiotoxicity.

Table 1
Management of high and very-high risk patients.

Cardiovascular diseases in patients at high or very-high risk of cardiotoxicity	Cardiac treatment	Oncology therapy	Multidisciplinary discussion between oncologist and cardiologist
Arterial thrombotic events (myocardial ischemia, peripheral artery diseases)	According to ESC guidelines in general population and ESC guidelines on cardio-oncology	Avoid drugs that can cause myocardial ischemia.	Evaluate the risks and benefits of cancer treatment; organize the most appropriate surveillance programme
Severe valvular diseases	Treat severe symptomatic valve diseases without delaying cancer treatment. Consider TAVI in frail cancer patients.	Avoid infusion of drugs that can cause volume overload in severe regurgitations	Evaluate the risks and benefits of cancer treatment; organize the most appropriate surveillance programme
Heart failure with reduced ejection fraction	According to ESC guidelines in general population and ESC guidelines on cardio-oncology	Avoid drugs that can cause heart failure	Evaluate the risks and benefits of cancer treatment; organize the most appropriate surveillance programme
Cardiomyopathy, myocarditis	According to ESC guidelines in general population and ESC guidelines on cardio-oncology	Avoid drugs that caused myocarditis, if therapeutic alternatives exist	Evaluate the risks and benefits of cancer treatment; organize the most appropriate surveillance programme
Venous thrombotic events	According to ESC guidelines in general population and ESC guidelines on cardio-oncology	Avoid drugs that can cause thrombosis	Evaluate the risks and benefits of cancer treatment; organize the most appropriate surveillance programme

For example, a study showed that dapagliflozin could be useful for preventing cardiotoxicity in diabetic cancer patients receiving Doxorubicin (Dox) treatment because Dapagliflozin effectively inhibited Dox-induced apoptosis and reactive oxygen species in cardiomyocytes under high glucose.[49]

Other studies in mice showed that empaglifozin reduced ferroptosis, fibrosis, apoptosis and inflammation in doxorubicin-treated mice, resulting in significant improvements in cardiac functions. Therefore, empaglifozin could prevent cardiotoxicity in non-diabetic cancer patients treated with doxorubicin but future studies are needed.

In patients with HFrEF, HF therapies must be optimized before considering a cardiac implantable device such as ICD or CRT (Table 1).

How to start anti-cancer drugs in patients with heart failure with reduced ejection fraction?

In cancer patients with HFrEF, before starting cancer treatment, it is necessary to identify the cause of the severe left ventricular dysfunction (if not known), without delaying the start of cancer therapy. Cardiac magnetic resonance or imaging stress test or coronary CT should be considered in this aim. Once discovered, the underlying cause of heart failure should be corrected without delay before starting cardiotoxic antineoplastic drugs.

HF medical therapy, with ACEI/ARB or sacubitril/valsartan, beta-blockers, mineralocorticoid receptor antagonist, dapaglifozin or empaglifozin, should be optimized to reduce the risk of HF hospitalization and death, before starting chemotherapy.[45–51]

Before starting cardiotoxic antineoplastic treatment in patients with HFrEF, when alternative effective non cardiotoxic treatment are not available, a multidisciplinary discussion in order to weigh the risks and benefits ratio of the oncological treatment and to select the less cardiotoxic drugs (e.g. example liposomal anthracyclines if the patient must necessarily undergo treatment with anthracyclines) should be performed. Moreover patients and caregivers should be informed about risks. A close follow-up is required during anti-cancer treatments in patients at very-high risk of cardiotoxicity.

When to use cardiac implantable device in cancer patients with HFrEF?

In patients with HFrEF, HF therapies must be optimized before considering a cardiac implantable device such as implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT).

In cancer patients, before implanting an ICD, the patient's life expectancy, functional status and prognosis should be considered. In addition, the cause of left ventricular dysfunction should also be considered, whether ischemic or post-chemotherapy.

In fact, the ESC Guidelines on heart failure recommend an ICD to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II-III) of ischaemic aetiology (unless they have had a MI in the previous 40 days), and an LVEF $\leq$ 35 % despite $\geq$3 months of optimized medical therapy, provided they are expected to survive substantially longer than 1 year with good functional status (class I, level of evidence A).

In patients with symptomatic HF (NYHA class II-III) of non-ischaemic aetiology and the same characteristics as above, an ICD should be considered (class IIa, level of evidence A).[45]

In fact, the benefit of ICD in patients with symptomatic HFrEF caused by coronary artery disease has been well documented; however, the evidence of the benefit of a prophylactic ICD implantation in patients with HFrEF of non-ischaemic aetiology is less strong, especially in the current era of new drugs for HFrEF and with the optimal use of disease-modifying therapies (betablockers, MRA, ARNI and SGLT2 inhibitors).[52] Therefore, in cancer patients, ICD should be considered only in selected cases of patients treated with first line cancer therapy and expected survival $>$ 1 year.[53] ICDs do not improve quality of life or heart failure symptoms. Indeed, because of the risk of complications, such as infections and inappropriate shocks, ICD may increase patient morbidity despite reducing mortality.

Conversely, CRT is recommended in cancer patients with HFrEF and other indications to CRT as recommended by ESC Guidelines[45] and treated with first line of cancer therapy, to reduce HF symptoms; CRT should be considered in selected cases of cancer patients treated with second line cancer therapy and good prognosis, to improve HF symptoms and LVEF.[53]

If, after multidisciplinary discussions, the cardiac device is implanted, it is necessary to assess the risk of thrombocytopenia and neutropenia caused by cancer therapy that may increase the risk of bleeding and infection, respectively. In addition, a multidisciplinary team should decide the timing of cancer treatments before and after device implant, to reduce risk of infection and bleeding.

How to start anti-cancer drugs in patients with cardiomyopathy, myocarditis and cardiac amyloidosis?

Patients with cardiomyopathy are patients at very-high risk of cardiotoxicity before starting anti-cancer drugs.[10]

Therefore, medical therapy optimization should be performed on the basis of the type of cardiomyopathy[54] before starting oncological treatment; a close follow-up should be organized.[8]

Certainly, it is important to perform an initial cardiological evaluation, to determine baseline LVEF before starting anti-cancer therapy and to stratify the cardiovascular risk[55] of the patient with previous myocarditis, to plan adequate follow-up and to decide the best cancer treatment after multidisciplinary discussion.

If myocarditis is caused by anti-cancer drugs (for example ICI), the cancer treatment must be stopped. Multidisciplinary discussion is recommended to review the decision on whether to restart cancer treatment. For example, after ICI-myocarditis, the resumption of cancer therapy depends on various factors including the severity of the ICI-associated myocarditis, alternative oncology treatment options, metastatic vs. adjuvant/neoadjuvant indication, and reducing from dual ICI to single ICI treatment if myocarditis was

triggered by combination ICI treatment.[8–56]

After a cardiotoxic event the best option would be the use of alternative, less cardiotoxic, oncological treatments.

Patients with multiple myeloma and amyloid light-chain cardiac amyloidosis (AL-CA) are at very high risk of cardiotoxicity.

Echocardiography surveillance every 3 cycles should be considered in high- and very high-risk patients receiving carfilzomib.[8]

Cardiovascular toxic effect of other drugs used to treat multiple myeloma should be carefully monitored in patients with AL-CA, for example venous thrombotic events in patients treated with immunomodulatory drugs (lenalidomide, pomalidomide, thalidomide) and arterial hypertension in patients treated with daratumumab, isatuximab.[8–57]

In fact, in patients with multiple myeloma and VTE-related risk factors, prophylactic doses of low-molecular weight heparins (LMWH) are recommended at least during the first 6 months of therapy; aspirin should be considered as an alternative to LMWH in patients with multiple myeloma with no risk factors or one VTE-related risk factor (excluding previous VTE) at least during the first 6 months of therapy; low doses of apixaban or rivaroxaban may be considered as an alternative to LMWH or aspirin.

Treatment with immunomodulatory drugs represents a VTE- related risk factor.[8]

Treatment of AL cardiac amyloidosis and its comorbidities should be performed in accordance with existing recommendations, avoiding volume overload after cancer therapy infusion and optimizing diuretic therapy in patients with heart failure with preserved LVEF.[58]

How to continue cancer treatment in patients with venous thrombotic events?

Venous thrombotic events (VTE) are common cardiovascular toxic effects of antineoplastic drugs, particularly VEGFi and other anti-cancer drugs.[26]

Patients with previous VTE are patients at high risk of cardiotoxicity, especially before starting VEGFi; at very-high risk of cardiotoxicity before starting immunomodulatory and proteasome inhibitors.[10]

In addition, cancer patients can develop venous thrombosis due to the cancer itself.[59]

VTE treatment in cancer patients should be performed with LMWH or direct oral anticoagulants (apixaban, rivaroxaban, edoxaban in patients without contraindications) for a minimum of 6 months. Prolongation of anticoagulation therapy beyond 6 months should be considered in selected patients with active cancer taking into consideration metastatic disease or chemotherapy use.[8–61]

Withdrawal of cancer treatment vs. continuation with ongoing anticoagulation is determined by the severity of thrombosis, cancer prognosis, and should be discussed with the patient. If VTE is caused by anti-cancer drugs, a multidisciplinary discussion is needed to evaluate alternative therapeutic strategies for the cancer; if there are no alternative strategies, anti-cancer treatment should be continued under close monitoring and prolonging the duration of anticoagulant therapy.

Conclusion

Treatment of high and very-high risk cancer patients is challenging in several conditions. A multidisciplinary discussion and a close collaboration between Oncologists and Cardiologists is fundamental to decide the best therapeutic option to treat cancer protecting the heart. Management of cancer patients with cardiovascolar diseases is complex and the treatment of cardiovascular complications should be guidelines-directed and should always take into account the presence of cancer. Preventive strategies should be used to avoid cardiotoxicity; medical treatment of cardiac disease should be optimized before, during and after anti-cancer treatment. Large multicenter randomized trials are needed to better address this challenging topic, being nowadays management mainly based on expert consensus.

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