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REVIEW
Cardiovascular disease

Management and treatment of cardiotoxicity due to anticancer drugs: 10 questions and answers

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Since the introduction of anthracyclines into clinical practice in the 1960s, chemotherapy has always been associated with cardiotoxicity. Patients on cardiotoxic drugs can develop a wide range of cardiovascular diseases, including left ventricular (LV) systolic dysfunction and heart failure (HF), arrhythmias, hypertension, and coronary artery disease (CAD). The rising number of cancer patients, population ageing, and the frequent overlap of cardiovascular and oncological diseases have highlighted the importance of close collaboration between cardiologists and oncologists. As a result, in 1995, cardiologists at the IEO (European Institute of Oncology) coined the term cardioncology, a new discipline focused on the dynamics of cardiovascular disease in cancer patients. Given the complex scenario characterized by a constant dialogue between the oncological condition and cardiovascular comorbidity, it is essential for the clinician to get the knowledge to properly fulfill the needs of the oncological patient under cardiotoxic treatment. Through the answer to 10 questions, we aim to describe the complex issue of cardiotoxicity by addressing the main critical points and current evidence related to the assessment, management, treatment, and surveillance of cancer patients under chemotherapy.

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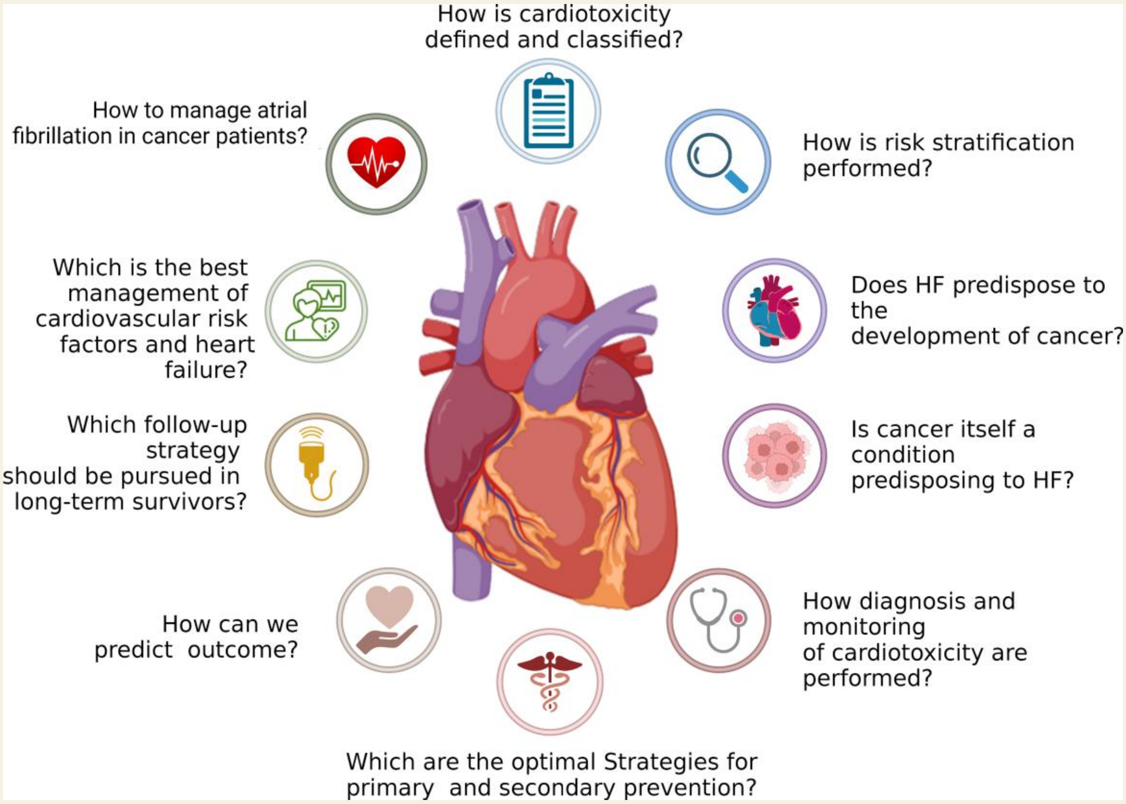
Graphical Abstract



Keywords Cardiotoxic • Cardiac biomarker • Ventricular function • Chemotherapy • Cardio protection • Heart failure

Introduction

The development of cardiotoxicity from antitumour drugs was first recognized in the early '60s, with the introduction of anthracyclines into clinical practice. Over the following decades, earlier diagnosis and advances in cancer therapy have led to a significant improvement of outcomes. The increasing number of cancer survivors, together with the use of combination treatments with synergistic cardiotoxic effects, makes cardiotoxicity a relevant limitation of many anticancer agents.

The manifestations of cancer drug cardiotoxicity are broad, including left ventricular (LV) systolic dysfunction and heart failure (HF), arrhythmias, hypertension, and coronary artery disease (CAD). Nonetheless, the current definition focus on cancer therapy-related cardiac dysfunction (CTRCD).[1]

Patients who are candidates to cardiotoxic therapies should be followed closely to detect a cardiotoxic damage before it becomes clinically evident. Echocardiography is a useful tool to assess parameters such as LV ejection fraction (LVEF) and global longitudinal strain (GLS), the latter to detect subclinical cardiac damage. Cardiac biomarkers, natriuretic peptides, and high-sensitivity (hs) troponins are gaining interest as they offer the possibility to detect cardiotoxic damage in an early phase and possibly to predict future development of CTRCD.[2,3]

In the present review, we will dissect the major principles of cardiotoxicity by answering 10 questions (*Graphical Abstract*), with the goal of providing a valuable tool for clinicians in managing patients who are at risk of developing cardiotoxicity. Given the many open issues in the field of cardionocology and the growing interest in this branch, we will try to bring the growing problem of cardiotoxicity from chemotherapy to the attention of non-specialist physicians so that they can provide proper treatment and prevention to their patients.

How is cardiotoxicity defined and classified?

The American Society of Echocardiography and the European Association of Cardiovascular Imaging (EACVI) have defined cardiotoxicity (or CTRCD) as LVEF decrease $\geq$10% to a value of <53%, as assessed by either two- or three-dimensional echocardiography, cardiac magnetic resonance (CMR), or multi-gated acquisition scan.[1]

Hypertension, vascular toxicity, cardiac dysfunction, myocarditis, and arrhythmias are the five basic signs of cardiotoxicity mentioned in the Intentional Cardio-Oncology Society (IC-OS) consensus statement.[4] Hypertension is identified as any increase in systolic and/or diastolic blood pressure following the start of cancer treatment, without any other contributory alterations, above the diagnostic threshold of 130/80 mmHg. Vascular toxicity, which comprises a variety of diseases (including stroke, peripheral ischaemia, thromboembolic event, etc.), is characterized by the induction or exacerbation of vascular pathology produced by chemotherapy. According to accepted criteria, vascular toxicity may be temporary or persistent, symptomatic or asymptomatic. Regarding the direct damage to the heart, cardiotoxicity is defined as any structural or functional cardiac abnormality brought on by the administration of anticancer therapy, whether asymptomatic or characterized by mild to severe symptomatology and clinical HF. Major and minor diagnostic criteria are used to define myocarditis, which can present as direct damage or immune-mediated inflammation of the myocardium in association with a variety of anticancer therapy. Finally, supraventricular and ventricular arrhythmias, determined by established standard practice, and/or QT prolongation may occur; according to the Fridericia formula, a prolonged QT interval >500 ms is defined as prolonged.

There are several classifications of cardiotoxicity, according to time of onset, clinical, echocardiographic, or biohumoral criteria. One of the first classifications of cardiotoxic drugs categorized them into Type I drugs, causing irreversible cardiac damage (such as anthracyclines), and Type II drugs, causing reversible cardiac damage (such as trastuzumab).[1] However, several studies conducted since 2011 have questioned this classification, demonstrating both the partial reversibility of Type 1 drug toxicity and the occurrence of some irreversible damage from Type 2 drug use.[2]

Cardiotoxicity can also be classified as acute or chronic, the latter being classifiable as early-onset or late-onset (*Table 1*). Using data from the Royal Brompton Hospital, a more recent classification of cardiotoxicity divides patients into six classes based on echocardiographic and biohumoral values as well as the presence or absence of symptoms.[5] In addition, the IC-OS has recently introduced a revised classification (*Table 1*).[4]

How is risk stratification performed?

It is common practice to assess the cardiovascular risk profile before starting cancer treatment. This can improve cancer outcomes by reducing interruptions in cancer treatment due to cardiovascular events, thus allowing a safer use of potentially cardiotoxic medications. Risk factors can be categorized as patient-related [demographic and age-related (<18 years and >65 years), life-style risk factors, cardiovascular history or risk factors; female gender; history] or treatment-related (regimens, doses, concurrent therapies). Treatment-related factors include high-dose chemotherapy, previous use of anthracycline, mediastinal radiation, and use of specific agents related to cardiotoxicity. All anthracycline doses are associated with a risk for developing HF, and cardiotoxicity may occur even at low doses.

Ghideon *et al*. developed a seven-factor risk score stratifying patients based on their risk of developing HF or cardiomyopathy over a 3-year period; the risk for cardiotoxicity can be classified as low (<20%), medium (21–39%), or high (>40%).[3] Patients at low risk should continue to receive the potentially cardiotoxic treatment under cardiovascular surveillance, according to international guidelines. Patients with a medium risk should have their cardiovascular health closely monitored during treatment or be referred to a Cardio-oncology or Cardiology evaluation. Patients with a high risk are referred to a Cardio-oncology or Cardiology evaluation, possibly in a Cardio-oncology specialist service, to optimize the management of their cardiovascular disease and modifiable risk factors. Of note, whether the use of such score could help to identify the patients which could benefit more from preventive therapies remains a key question to be addressed by future dedicated studies.

Herrmann *et al.*[6] have proposed the Cardiotoxicity Risk Score, a model that assesses both patient- and treatment-related risk factors. Scale values range from 0 to 4, in an increasing order of risk. Currently, there are not sufficient data to include these risk scales into routine clinical practice; none of these risk scores has been prospectively validated and there is a need for future studies to clarify their reliability. It would also be useful to promote the introduction of electronic tools or apps for risk stratification to be used in clinical practice. Finally, proteomic methods could allow a better profiling of patients who may be at low risk but have shown susceptibility to complications during follow-up.

Does heart failure predispose to the development of cancer?

Several studies have shown that patients with HF are at higher risk of developing cancer.[7,8] Heart failure and cancer share common risk factors, such as ageing, male sex, obesity, diabetes mellitus, sedentariness, and smoking.[9] They might both be induced by a common systemic disturbance, and HF might promote cancer development.[7] Inflammation and oxidative stress are two of the main pathways involved in the etiopathogenesis of cancer and HF, promoting a tumourigenic microenvironment, and cancer invasiveness. Moreover, increased activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS) have been also shown to promote several steps in cancer development.[7] Some cardiac stress biomarkers, such as *n*-terminal pro-B-type natriuretic peptide (NT-proBNP), have been shown to be related to cancer disease progression and severity.[8] Additionally, HF is associated with enhanced tumour growth; this could be caused by cardiac excreted factors, such as SerpinA3, which could stimulate tumour growth via the Akt pathway.[7] In turn, cancer development may impair the precarious homeostasis of HF patients, increase their risk of developing CRTCD, and worsen their prognosis.[9]

Is cancer itself a condition predisposing to heart failure?

Cancer itself might represent a condition at increased risk of developing HF.[10] Cancer-related inflammation and oxidative stress might support the development of cardiac damage by sustaining microvascular endothelial dysfunction.[11] Furthermore, increased RAAS activity and autonomic dysfunction due to cancer might foster HF progression.[12] Preclinical studies have also shown that several oncometabolites (e.g. D-2-hydroxyglutarate) may promote cardiac dysfunction.[13] An active cancer has been associated with raised levels of cardiac biomarkers in treatment-naïve cancer patients, and this increase predicts adverse outcomes.[8] Untreated cancer patients often display an initial impairment of ventricular structure and function,[14] autonomic dysfunction,[12] and reduced exercise capacity with a marked reduction in peak oxygen consumption.[15]

Despite the growing interest in the subclinical cardiac damage in cancer patients before antineoplastic treatments, further studies are needed to assess the subclinical cardiac damage in cancer patients naïve to chemotherapy, possibly using cardiac biomarkers or CMR.

Table 1 Old and new classification of cardiotoxicity[2,4,5]

Type of damage	Onset	Clinical manifestation	Reversibility	Dose correlation
Acute cardiotoxicity	Within 2 weeks after chemotherapy	↓myocardial contractility	Usually reversible	Unknown
Early-onset chronic cardiotoxicity	Within 1 year after chemotherapy	Dilated-hypokinetic cardiomyopathy	Usually irreversible	Dose dependent
Late-onset chronic cardiotoxicity	>1 year after chemotherapy	Dilated-hypokinetic cardiomyopathy	Usually irreversible	Dose dependent

Type of damage	Imaging		Biomarker	Symptomatic
Royal Brompton Hospital classification				
Early biochemical cardiotoxicity	Normal		↑BNP/cTn	No
Early functional cardiotoxicity	↓GLS[a]/III–IV diastolic		Normal	No
Early mixed no cardiotoxicity	↓GLS/III–IV diastolic dysfunction		↑BNP/cTn	
Symptomatic HF with preserved EF	↓GLS/III–IV diastolic dysfunction		↑BNP/cTn	Yes
Asymptomatic LVD	↓LVEF <50% ↓LVEF >10% to an LVEF <55%		↑BNP/cTn	No
Symptomatic LVD	↓LVEF <50% ↓LVEF >10% to an LVEF <55%		↑BNP/cTn	Yes
IC-OS 2021 consensus asymptomatic CTRCD				
Mild	↓LVEF ≥ 50% ↓GLSa >15%	And/or	↑BNP/cTn	No
Moderate	↓LVEF ≥10% to an LVEF of 40–49% ↓LVEF <10% to an LVEF of 40–49% and ↓GLS >15%	And/or	↑BNP/cTn	No
Severe	↓LVEF < 40%			No
Symptomatic CTRCD				
Mild	↓LVEF ≥ 50% ↓GLS >15%	And/or	↑BNP/cTn	Mild HF symptoms, no intensification of therapy required
Moderate	↓LVEF ≥10% to an LVEF of 40–49% ↓LVEF <10% to an LVEF of 40–49% and ↓GLS > 15%	And/or	↑BNP/cTn	Moderate symptoms need for and intensification of diuretic and HF therapy
Severe	↓LVEF < 40%			The extent of symptoms requires hospitalization for HF
Very severe				Requiring inotropic support, mechanical circulatory support or consideration for transplantation

BNP, brain natriuretic peptide; cTn, cardiac troponin; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction.
[a]The decrease in GLS is considered in absolute values.

Diagnosis and monitoring of cardiotoxicity

Which are the imaging techniques used to study cardiotoxicity?

Echocardiography and CMR are the most widely used, with some limited use of nuclear imaging, namely positron emission tomography, when CMR is not an option.

Left ventricular ejection fraction reduction is not a sensitive measure of cardiotoxicity, and changes in myocardial deformation occur before a decline in LVEF or symptomatic HF; a treatment strategy based on changes in LVEF, risks of delaying a timely diagnosis, and subsequent treatment. Global longitudinal strain has been proposed as a potentially strong and sensitive diagnostic and prognostic marker of subclinical ventricular dysfunction.[1] A drop in the absolute value of strain ranging from 10 to 15% indicates cardiotoxic injury. An echocardiographic screening was conducted comparing GLS-based approach with a standard LVEF-based approach in high-risk patients. However, no difference was seen in LVEF or GLS at 1 year.[16] Although impaired LV systolic function holds diagnostic and prognostic significance, an ideal echocardiographic parameter has not been found yet.

The introduction of CMR into routine clinical practice may be helpful in patients with poor acoustic window or when echocardiographic and clinical findings are discordant. As an alternative to ultrasound data, comprehensive tissue characterization provided by CMR could assist in identifying early forms of cardiotoxicity before major structural damage. The evidence has been conflicting up to this point, and their routine clinical use is still constrained by their restricted availability and high cost.

Is there a defined biomarker-based approach?

Biomarkers offer a promising complementary tool to imaging techniques for cardiotoxicity surveillance[17–19](*Table 2*).

The most studied biomarkers of cardiac injury in cardio-oncology are cardiac troponins (cTn) and NPs. After anthracycline-based chemotherapy, cTn elevation often precedes changes in LVEF,[18] and troponin I is a predictive marker of occurrence and severity of cardiotoxicity, both in patients treated with anthracyclines[3] and those on combination regimens, including trastuzumab.[2] Moreover, troponin I has a 99% negative predictive value for cardiotoxicity.[3] High-sensitivity cTn assays have the potential for an even earlier detection of acute cardiotoxicity.[19]

B-type natriuretic peptide and NT-proBNP are markers of increased LV wall stress routinely used for the diagnosis and management of HF. Their measurement allows to assess the risk of cardiotoxicity and help determine the degree of cardiac dysfunction.[17] However, there is a significant heterogeneity across studies in terms of biomarker assays, cut-off values, and timing of measurement.[18] Moreover, NP levels should be interpreted based on advanced age, female sex, kidney disease, and cancer itself.[20]

Markers of cardiac remodelling such as soluble suppression of tumourigenesis-2, galectin-3, and growth differentiation factor-15, have not demonstrated to be effective in predicting cardiotoxicity[17,19] as well as biomarkers of inflammation[17] (*Table 2*). In contrast, myeloperoxidase, a marker of oxidative stress,[11] has shown additive value compared with hsTnI for predicting cardiotoxicity in patients receiving doxorubicin and trastuzumab.[19]

Several studies have shown promising results for microRNA use in cancer patients treated with anthracyclines.[18] In particular, miR-1 has shown to predict doxorubicin-induced cardiotoxicity in breast cancer patients with greater accuracy than cTnI.[18]

Large prospective studies with long-term follow-up are needed to standardize both the timing of sampling and the assay methods to detect specific biomarkers for different cancer therapies.[19]

How should imaging techniques and biomarkers be combined?

Imaging parameters and biomarkers of cardiac damage have intrinsic limitations when used alone for cardiotoxicity surveillance. Indeed, structural changes are not suitable for early detection of cardiotoxicity, whereas biomarkers such as hs-cTn are not specific for CTRCD. A hybrid strategy combining circulating biomarkers and non-invasive cardiac imaging may overcome the limitations of the use of a single approach, potentially allowing an even earlier detection of cardiotoxicity.

A study on 81 women with breast cancer treated with cardiotoxic chemotherapy showed that a combination of >19% decrease in peak longitudinal strain and >30 ng/L increase in hsTnI after a 3-month therapy had a 93% specificity (vs. 73% for each parameter alone) for prediction of cardiotoxicity.[21] Based on these preliminary results, the EACVI has suggested an integrated approach including the assessment of LVEF, GLS, and cTn levels at baseline and during follow-up.[1]

Despite some promising results, there is no solid evidence about a multimodal approach to cardiotoxicity surveillance. In particular, it is unknown which combination of imaging parameters and biomarkers holds the best positive and negative predictive values to detect cardiotoxicity, the optimal timing for evaluation, and the possibility to predict late cardiotoxicity.

Which are the optimal strategies for primary and secondary prevention?

According to the 2016 ESC Position Paper on Cancer Treatments and Cardiovascular Toxicity, the only primary prevention strategies valid for all types of chemotherapy are treatment of comorbidities and cardiovascular risk factors. To mitigate anthracycline toxicity, dose reduction, use of liposomal formulations or continuous infusion is recommended.[22,23] (*Table 3*). To date, dexrazoxane is the only drug specifically approved for the primary prevention of anthracycline-related cardiotoxicity.[22] Its use is currently approved for adults with advanced metastatic breast cancer who have received a cumulative dose $\geq$300 mg/m^2 of doxorubicin or $\geq$540 mg/m^2 of epirubicin, and it is no more contraindicated for children requiring chemotherapy with high cumulative dose (>300 mg/m^2) of doxorubicin or the equivalent dose of another anthracycline.[24]

As shown in Supplementary material online, *Table S1*, several studies have suggested potential advantages for LVEF recovery and cardioprotection associated with the use of BBs and RAAS inhibitors. Despite the positive findings, the significant heterogeneity between the studies is a significant limitation.[25] Moreover, only a small number of drugs in the studied pharmacological classes appear to have a significant cardioprotective effect. To date, only two clinical studies have examined the use of MRAs thus far, investigating the effectiveness of spironolactone[26] and eplerenone[27] in preventing cardiotoxicity. The beneficial effects of statins in preventing HF in patients receiving anthracycline are being tested. Future research should clarify the possible clinical relevance and applicability of therapies acting on pro-oxidant and pro-inflammatory pathways specifically involved in cardiotoxicity.[28]

Secondary prevention includes the use of medical therapies in patients who have developed a cardiotoxic damage, possibly identified through imaging and/or biomarkers. According to the ESC Position Paper,[22] a cardioprotective strategy based on the administration of one or more guideline-based HF treatments is advised in patients with a considerable drop in LVEF, especially if it is accompanied by a shift in natriuretic peptides. In patients

Table 2 Main biomarkers used for early detection of cardiotoxicity and under investigation[18,19]

Circulating biomarkers	Cut-off	Advantage	Disadvantage
Troponin			
• Conventional troponin I and T	• ≥80 ng/L • ≥30 ng/L	• Widespread and cost-effective • Commonly studied • Possibly predictive of a future decline in LVEF	• Unknown optimal timing • No optimal threshold for risk stratification • No sure associations with cardiotoxicity risk • Influence of renal function
• High-sensitive troponin I and T	• Absolute δ 7–9,2 ng/L	• More sensible • Possibly detection of acute cardiotoxicity	• Less specific • Higher rate of false positives • Discrepancies between different assay platforms
Natriuretic peptides			
• BNP	• 100 pg/mL [a]	• Widely available • Gold-standard for clinical HF	• Unknown optimal timing • No optimal threshold for risk stratification
• NT-proBNP	• 125 pg/mL [a]	• Potential indicators of late cardiotoxicity	• No sure associations with cardiotoxicity risk
Biomarkers under investigation			
• Galactin-3			• No significant association with cardiotoxicity
• ST-2			• No sufficient data
• GDF-15		• Possibly detection of late anthracycline cardiotoxicity in paediatric cancer survivors	• Need for further studies
• CRP	• ≥ 3 mg/L	• Possibly use with T-cell therapies (CAR)	• Poor specificity • No significant association with cardiotoxicity
• MicroRNA (miR-1, miR-133, miR-208, miR-499)	• Up-regulation compared with baseline	• Present in multiple body fluids • Remain stable under extreme temperatures and pH • Have long half-life • Can be measured using different methods • More sensitive than TnI for predicting the risk of cardiotoxicity	• Expensive • Not widespread • Needs further study
• MPO	• Rise in MPO levels from baseline to ≥3 months	• Associated with risk of anthracycline and trastuzumab cardiotoxicity • Predictive of increased cardiotoxicity risk over the end of treatment	• Limited data • Sensitive to processing condition

BNP, brain natriuretic peptide; CRP, C-reactive protein; GDF-15, growth differentiation factor-15; PO, myeloperoxidase; NT-proBNP, n-terminal pro-brain-type natriuretic peptide.
[a]BNP and NT-proBNP levels are significantly higher in atrial fibrillation patients compared with the rest of the general population.

with subclinical heart injury, however, there is no indication for any form of cardioprotective therapy. If HF occurs while receiving chemotherapy, the patient should be managed in accordance with the most recent ESC recommendations for HF. According to the oncology team, stopping the medication until the patient reaches clinical stability is advised if cardiotoxic treatment is interrupted.

How can we predict outcome?

Anthracycline-induced cardiomyopathy occurs in up to 10% of cancer survivors with 98% of cases occurring within the first year of anthracycline exposure.[22] An LVEF <40% in patients with severe cardiotoxicity correlates with a 10-fold increase in total mortality, while there is no agreement on the impact on mortality of LVEF values between 40 and 50%.[29] A decline in LVEF, either symptomatic or not, predicts a worse outcome: for example, at a 3.5-year follow-up, asymptomatic LVEF decline in patients treated with anthracyclines is associated with increases in adverse cardiac events.[3] An early treatment is more likely to induce LVEF recovery, which is associated with a reduction in adverse cardiac events.[30]

Patients experiencing a persistent increase in cTn during anticancer treatment have a higher risk of subsequent LV dysfunction,[3] and a prompt therapy with enalapril could change the natural development of cardiotoxicity.[31] Nevertheless, patients with abnormal biomarkers

Table 3 **Primary prevention strategies suggested by ESC**[23]

Chemotherapy drug	Potential cardioprotective measure	Cardioprotective mechanism	Clinical benefit	Disadvantages/ limitations
Any type of chemotherapeutic drug	Treatment of cardiovascular risk factors	Reduced cardiac stress	Reduced incidence of HF	None
	Correction of comorbidities	Reduced cardiac stress	Reduced incidence of HF	None
Anthracyclines	Liposomal formulations	Limited trans-endothelial cardiac diffusion of the drug	Does not change the effectiveness of the drug increased cardiac tolerance	High costs
	Continuous infusions	Reduction of the maximum blood concentration of the drug (C_{max})	Maintenance of drug activity reduced exposure of the heart to anthracyclines	Prolonged hospitalization lack of long-term protection in some paediatric settings
	Use less cardiotoxic analogues, and respect cumulative dose limits	Reduction of ROS production and oxidative stress intensity	Reduced incidence of HF	Not definitely proven[a]
	Dexrazoxane	Iron chelation enhances the profile of oxidative stress inhibition of cardiomyocyte apoptosis by hindering the binding of anthracyclines to topoisomerase IIβ	Reduced risk of HF well-tolerate	Reduces the efficacy of anthracyclines

[a]About the use of less cardiotoxic analogues.

(cTn and NT-proBNP) but LVEF ≥50% did not show a poor outcome.[29]

Overall, the optimal use of imaging and laboratory techniques to predict outcomes remains to be defined.

Which follow-up strategy should be pursued in long-term survivors?

A consensus about long-term cardiomyopathy surveillance strategies for childhood cancer survivors has stated that surveillance should start no later than 2 years following the end of cardiotoxic therapy and be repeated every 5 years.[32]

In 2013, Carver *et al.* proposed a screening algorithm for asymptomatic adult cancer survivors, based on four points: prior cancer therapy, risk factors (including age >65 years, female sex, obesity, hypertension, etc.), functional status at baseline and follow-up visits, and cardiac structure. All survivors are recommended to undergo echocardiogram (ECG) and BNP measurement at baseline. Even if all three are normal, the patient is considered at risk of HF (Stage A), and a re-evaluation every 2 years with clinical history, physical examination, and BNP measurement is recommended, as well as an ECG every 5 years. Patients with an abnormal ECG at baseline are considered Stage B, and re-evaluation every 6 months is advised.[33]

Nowadays, recommendations for after-anticancer therapy evaluations vary according to the single patient.[34] For asymptomatic patients who have normal cardiac function, periodic screening for the development of LV dysfunction should be considered at 6, 12 months, and 2 years post-treatment and periodically thereafter. For patients who developed asymptomatic LV dysfunction or HF, regular cardiology evaluation should be continued indefinitely, regardless of the improvement in LVEF or the presence of symptoms. Finally, for patients with a history of mediastinal chest radiotherapy, evaluation for CAD and valvular disease is recommended, starting at 5 years post-treatment, and then every 3–5 years.

Which is the best treatment for cardiovascular risk factors and heart failure?

The use of BBs and/or an angiotensin antagonist for the treatment of arterial hypertension should be preferred since these drugs have shown additional cardioprotective effect during anthracyclines and/or trastuzumab treatment.[35] A pre-existing diagnosis of HF does not necessarily exclude treatment with potential cardiotoxic anticancer therapies, but rather allocates the patient in a high-risk category requiring cardioprotective treatment and close monitoring.[36] Patients developing HF with reduced ejection fraction during or after-anticancer treatment should receive standard HF care according to the current guidelines.[36] For patients with an important reduction of LVEF (<40%) and without at least partial recovery after cardioprotective therapy, continuation of anticancer therapies known to be cardiotoxic is not recommended,[6] unless there are no alternative anticancer treatment effective options.

The best timing for the start of an early cardioprotective treatment should be evaluated based on change in cardiac function, alteration of cardiac markers (cTn and NPs) and cardiovascular comorbidities. Starting ACEi and BBs is highly suggested even in asymptomatic patients with an initial alteration of myocardial deformation at speckle imaging or with a rise of cTn, even if LVEF is preserved.[34] Early ACEi initiation in patients with elevated cTnI prevents late development of cardiomyopathy and HF.[25]

Little is known about long-term outcomes and prognosis for cancer patients who have recovered from cardiac dysfunction, and the need for continuing HF medications after recovery. It is reasonable to recommend to withdraw HF therapy only after a period of stability, and in absence of other cardiac risk factors and ongoing anticancer therapy.

How to manage atrial fibrillation in cancer patients?

Atrial fibrillation (AF) is common in patients with cancer,[37] independently of the type of malignancy,[38] with an incidence of 17.4 per 1000 person-years vs. 3.7 per 1000 person-years in the general population.[38]

The management of AF in cancer patients poses specific challenges; AF is *per se* a condition favoring hypercoagulation within the heart, hence anticoagulation is mandatory in most cases.[39] Nonetheless, current guidelines do not provide clear-cut recommendations on the optimal thrombo-prophylaxis strategy in cancer patients. Moreover, commonly employed scores to evaluate the balance between thromboembolic and bleeding risks of AF (namely, CHA_2DS_2-VASc and HAS-BLED) have not been validated in patients with cancer.[22] Low molecular weight heparin is often preferred over warfarin in cancer patients because of the risk for significant variations in the international normalized ratio.[39] As for non-vitamin K antagonist oral anticoagulants (NOACs), data on their role in the prevention of AF-related stroke and systemic embolism are limited.[40] A meta-analysis showed how the use of NOACs in patients with AF and cancer resulted in lower or similar rates of thromboembolic and bleeding events compared with warfarin.[41] However, caution should be taken when prescribing NOACs to patients undergoing chemotherapy, due to the possible occurrence of drug–drug interactions with new anticancer treatments.[40] Moreover, NOACs therapy should be re-evaluated whenever a patient is scheduled for a cycle of myelosuppressive chemotherapy or radiotherapy, given that they might determine a reduction in the platelet count, renal/liver function, and vascular integrity.

As for medical management of AF in cancer patients, the ESC Position Paper on cancer treatments and cardiovascular toxicity recommends an individualized approach regarding the choice between rate or rhythm control.[22] Rate control can be achieved with beta-blockers, non-dihydropyridine calcium channel blockers, and, in selected cases, digitalis (especially in patients with HF).[22] Concerning rhythm control, advances in ablation techniques and the introduction of new-generation catheters have simplified percutaneous ablation procedures and extended their use to more complex scenarios. There is initial evidence on the possibility of performing percutaneous pulmonary vein isolation in patients with active cancer or previous history of cancer, apparently showing good arrhythmia-free survival rates, but with conflicting results in terms of safety, especially regarding the risk of periprocedural bleeding.[42–45] Future large, dedicated studies should clarify whether percutaneous AF ablation is associated with a prognostic and/or symptomatic benefit in cancer patients.

Conclusion

Cardioncology is a relatively young and developing field of study; given the extensive overlap between cancer and cardiovascular diseases, the management of the cancer patient receiving cardiotoxic treatments is a particularly complicated and multifaceted subject. We attempted to give the physician the skills they need to interact with the field of cardioncology by responding to 10 questions on the subject of cardiotoxicity, ranging from the description of cardiotoxic damage to therapy and follow-up measures in cancer survivors. The major crucial issues of cardiotoxicity detection, treatment, and patient outcome are lacking clear data, necessitating additional research to support, enlarge, and integrate the body of knowledge currently known about cardiology.

Author contributions

M.C., I.F., A.D.F., and D.M.C. contributed to the conception of the review, the bibliographic research, and the drafting of the manuscript. A.G., A.A., C.G., C.P., V.C., C.P., F.G., C.M.C., and M.E. contributed to critical revision and editing. M.C. designated tables and figures. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Supplementary material

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