Belgian guidelines on supportive care: Cardiotoxicity of cancer treatments

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SUMMARY

Increasing effectiveness of cancer treatments significantly improved patient survival. More treatment options are available for frailer patients. Therefore, the importance of appropriate supportive care measures increases, particularly in high-risk patients. More data concerning potentially cardiotoxic effects of cancer therapies are available, involving multiple cardiovascular side-effects. We provide an overview of available strategies to identify the patient at increased risk for cardiotoxicity, to prevent, detect and treat cardiotoxic effects of cancer treatments and to organise follow-up in patients with documented toxicity. The main focus will be left ventricular dysfunction and heart failure, but some other frequently encountered forms of toxicity will be discussed.
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INTRODUCTION

Cardiovascular disease (CVD) and cancer cause >50% of all deaths in Belgium.[1] Shared pathophysiological mechanisms are suspected, and common risk factors have been established.[2,3] This implies that cancer patients are at risk for the development of CVD, confirmed by the fact that many cancer survivors die of CVD rather than of recurrent cancer.[4] Cancer therapies may cause multiple cardiovascular toxicities, requiring particular attention and treatment, before, during and after treatment completion.

While cardio-oncology is not (yet) a formally registered subspecialty in Belgium, international postgraduate courses are being organised. Interest and awareness are steadily growing and an increasing amount of hospitals incorporate a dedicated cardio-oncology consultation in their clinical activities, often led by a non-invasive cardiologist or heart failure specialist.

IDENTIFYING THE PATIENT AT RISK FOR CARDIOTOXICITY

Identifying patients at risk for cardiotoxicity is paramount, requiring insight into cardiotoxic side-effects of planned therapies, and into the patient's pre-existing cardiovascular (CV) risk profile and comorbidities.[5,6] Optimising CV care and risk factor management increases the proportion of patients completing cancer therapy, without interference of new or worsening CVD.[5] Baseline CV risk evaluation should be completed early and should not delay cancer treatment initiation, unless a (very) high risk profile is identified.[5] The latter does not necessarily imply treatment exclusion, but warrants a multidisciplinary discussion between treatment partners after cardio-oncological evaluation, balancing efficacy, safety, CV risk and cancer treatment benefit.[5]

PRE-TREATMENT CARDIOLOGICAL EVALUATION AND PRIMARY PREVENTION

Baseline CV risk in cancer patients consists of lifestyle and medical CV risk factors, pre-existing CVD, previous cardiotoxic treatment and cardiac biomarkers (*Table 1*).[5,6] Risk assessment should cover cardiac and cancer history, including CV risk factor optimisation (blood pressure, dyslipidaemia and glycaemic management, smoking cessation and weight reduction) (*Table 1*).[6] Baseline biomarker status should be

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TABLE 1. Baseline comprehensive cardiovascular risk assessment. Adapted from Lyon et al, Eur J Heart Fail. 2020 and Zamorano et al, Eur Heart J. 2016.[5,6]

Risk factors contributing to baseline CV risk in cancer patients	
Medical CV risk factors	- Age : <18 years, >50 years (trastuzumab), >65 years (anthracyclines) - Family history of premature CVD - Arterial hypertension - Hypercholesterolaemia - Diabetes mellitus
Lifestyle CV risk factors	- Smoking - Alcohol abuse - Obesity - Sedentarity
Cardiac biomarkers	Cardiac troponin + BNP / NT pro-BNP
Previous cardiotoxic cancer treatment	- Previous anthracyclines (cumulative dose) - Previous radiotherapy (total dose, fraction dose).
Previous CV disease → ECG → Echocardiogram	- Heart failure - Coronary artery disease : previous MI, PCI, CABG - Moderate / severe valve disease with LV hypertrophy or impairment - Hypertensive, hypertrophic, dilated, restrictive, infiltrative cardiomyopathy - Significant arrhythmias (ventricular tachyarrhythmias, atrial fibrillation)

BMI; body mass index, BNP; brain natriuretic peptide, CABG; coronary artery bypass graft, CVD; cardiovascular disease, LV; left ventricular, MI; myocardial infarction, NT pro-BNP; N-terminal pro-brain natriuretic peptide, PCI; percutaneous coronary intervention.

considered (cardiac troponin and natriuretic peptides) (*Table 1*) (level of evidence III, A).[6] Risk stratification proformas are available for several treatment categories, allowing stratification into low, medium, high or very high-risk category (*Table 2*).[5] For low-risk patients (<2% cardiotoxicity risk), cardiological follow-up per standard protocol is sufficient.[5] Medium-risk patients require closer follow-up, focused on primary prevention (2-9% toxicity risk).[5] In (very) high risk patients (10-19% toxicity in high risk, >20% in very high risk patients), dedicated cardio-oncological evaluation, including risk factor optimisation, electrocardiogram (ECG) and echocardiography, is mandatory to evaluate treatment feasibility, with patient-tailored follow-up.[5] The ECG should be scrutinised for QTc-prolongation, arrhythmia and ischaemia.[6,7] Echocardiography should include LV function assessment, valvular status and detection of right ventricular or pericardial disease.[6,7,8]

Cardioprotective treatment (CPT) is debated, suggesting moderate benefit of ACE-inhibitors (ACEi, *e.g.* enalapril 5 to 20mg once daily, lisinopril 5 to 20mg once daily) and beta-blockers (BB, *e.g.* carvedilol 6.25 to 25mg twice daily, nebivolol 5mg once daily), evidence being limited by small trial populations, including many low-risk patients, different anticancer therapies and trial endpoints (level of evidence II, B).[7]

ON-TREATMENT FOLLOW-UP

SURVEILLANCE STRATEGY

Cardio-oncology follow-up during cancer treatment depends on the type of cancer treatment, and individual cardiotoxicity risk.[5,6] Using the above-mentioned risk stratification proformas, low-risk patient undergo standard follow-up.[5] Medium-, high- and very high-risk patients require tailored follow-up.[5] Follow-up consists of clinical evaluation, ECG, echocardiography, and risk factor management. Any intervention should be based on this multimodal approach.[6]

Increased baseline biomarker values identify patients with higher risk of toxicity (level of evidence III, A).[7,9] Biomarker follow-up may be valuable, but currently proposed strategies are expert opinion-based: further investigations are required, and due to low specificity, should be interpreted cautiously, taking into account pre-existing CVD.[7,9]

Imaging follow-up consists of echocardiography unless image quality is prohibitive: baseline evaluation should be comprehensive, serial re-evaluations may be targeted towards left ventricular ejection fraction (LVEF) and diastolic function. Timing intervals are defined for different treatment strategies for low, medium, and (very) high risk populations.[8]

TABLE 2. Cardiotoxicity risk categories and definitions in baseline risk stratification. Adapted from Lyon et al, Eur J Heart Fail 2020.[5]

Risk category	Definition
Low risk	Risk of cardiotoxicity ≤**2%**
	Absence of risk factors for cardiovascular toxicity OR Presence of 1 single-point intermediate risk factor
Intermediate risk	Risk of cardiotoxicity **2-9%**
	Presence of >1 intermediate risk factor, points totalling 2-4
High risk	Risk of cardiotoxicity **10-19%**
	Presence of ≥ 1 high risk factor for cardiovascular toxicity OR Presence of multiple intermediate risk factors, points totalling ≥5
Very high risk	Risk of cardiotoxicity **>20%**
	Presence of ≥ 1 very high risk factor for cardiovascular toxicity

Baseline cardiotoxicity risk assessment takes into account patient-related as well as therapy-related factors contributing to the cardiovascular risk. These risk factor classes are specifically defined for each of the seven treatment groups for which a stratification proforma is available: anthracycline chemotherapy, HER2-targeted cancer therapy, vascular endothelial growth factor inhibitors, tyrosine kinase inhibitors for CML, proteasome inhibitors and immunomodulatory agents in multiple myeloma, combination RAF/MEK-inhibitors and androgen deprivation therapies. Intermediate, high and very high risk factors are specified for each of the above-mentioned treatments and can be found in the cited reference.[5] Evidence for defining the absolute risk is limited, cardiotoxicity risk groups are defined based on discussion and expert opinion. These risk strata function as a guide, more studies are required for further validation and refining of the current ranges. *CML; chronic myeloid leukaemia, HER2; human epidermal growth factor receptor 2, RAF/MEK; rapidly accelerated fibrosarcoma B-type / mitogen-activated extracellular signal-regulated kinase inhibitors.*

ASYMPTOMATIC LVEF REDUCTION

'Cardiotoxicity' is defined as an absolute reduction of LVEF of >10% compared to baseline, resulting in LVEF <50%.[6,10] Earlier detection and treatment improve reversibility of new-onset left ventricular dysfunction (LVD) and cardiac event-free survival, implying a low threshold for cardio-oncology consult and initiation of heart failure (HF) therapy (ACEi and BB) in any patient with new LVD.[6,7] *Figure 1* summarises the currently recommended approach. Absolute LVEF reduction of <10%, with LVEF >50% does not require treatment interruption: CPT (ACEi + BB) may be considered.[7] For asymptomatic LVEF between 40% and 50% under anthracyclines, withholding treatment should be considered until LVEF recovers.[7] If LVEF drops below 40% under anthracyclines, alternative treatment is required.[6,7] Anti-HER2 treatments and most targeted therapies can be continued under HF therapy as long as LVEF >50%, with cardio-oncology supervision.[6,7] In LVEF <40%, a non-cardiotoxic treatment should be given and HF therapy initiated.[6,7] Absolute decrease in LVEF of ≥20% requires treatment pause until optimisation of HF therapy and performance of further investigations.[7]

NEW CARDIOVASCULAR SYMPTOMS

Every cancer patient developing symptoms suggestive of CVD, before, during or after treatment, deserves cardio-oncological evaluation (*Figure 1*).[6,7] For patients undergoing oncological treatment, withholding treatment is recommended until cardiac evaluation and stabilisation.[7] In symptomatic LVEF reduction, HF therapy should be initiated and optimised.[7] For new symptoms of HF with preserved LVEF, stabilisation (recompensation) is mandatory prior to treatment resumption.[7] In both cases, short term re-evaluation (3-4 weeks) is recommended.[6,7] Treatment resumption is discouraged if the cardiotoxicity developed on anthracycline therapy (cascade effect) or if LVEF does not recover above 40%.[7] In these cases, less cardiotoxic therapy should be considered.[7] Biomarkers may be valuable in these cases, but formal guidelines are not yet available.

GLS AND/OR BIOMARKERS ALTERATIONS

LVEF reduction may be preceded by GLS alterations, although not every GLS reduction implies cardiotoxicity.[6,7,8] GLS has a superior predictive value for impending cardiotoxicity compared to LVEF, which is hampered by poor sen-

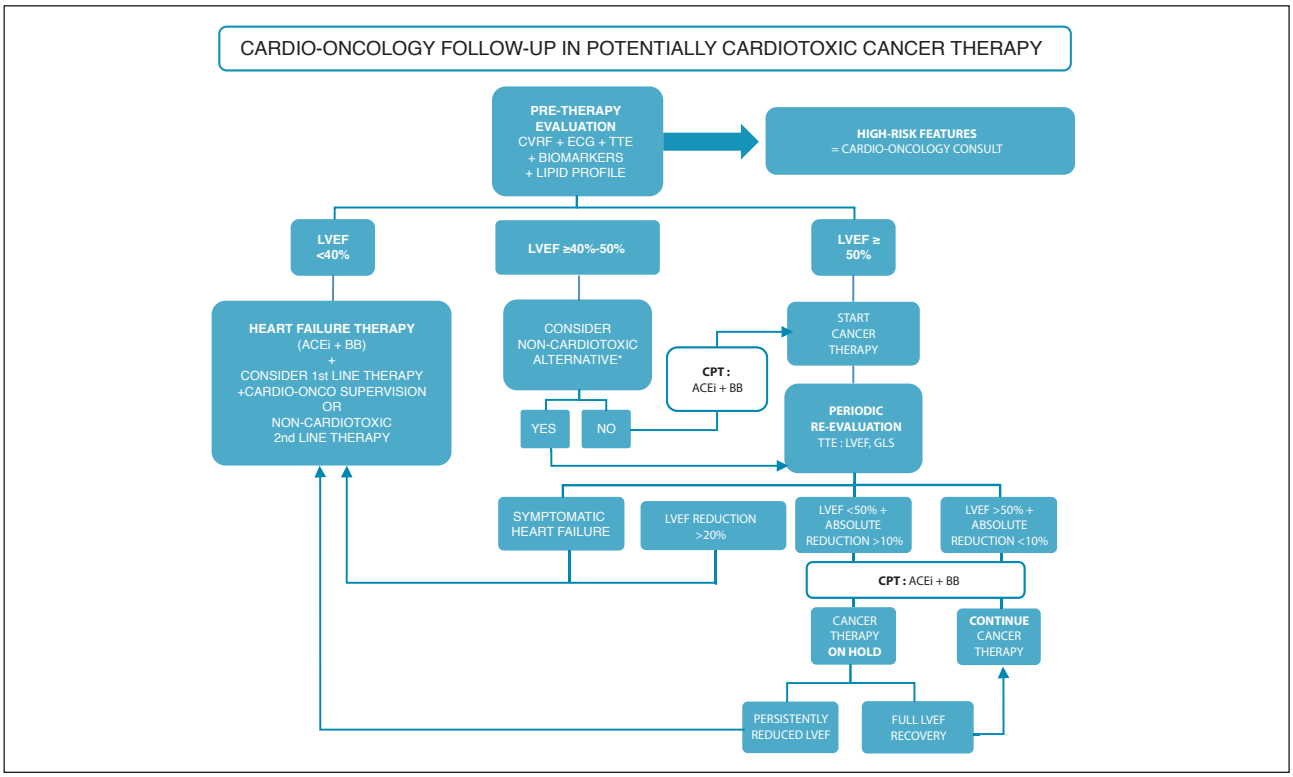

FIGURE 1. Follow-up of potentially cardiotoxic cancer therapy. Adapted from Curigliano et al, Ann Oncol 2020.[7]
Baseline cardiological evaluation prior to cancer treatment initiation is paramount. Periodic re-evaluation intervals vary, depending on cancer treatment and CV status of the patient.
A multidisciplinary approach between cardiologist and oncologist is necessary when discussing treatment alterations.
ACEi; angiotensin-converting enzyme inhibitor, BB; beta blocker, CVRF; cardiovascular risk factors, CPT; cardioprotective therapy, ECG; electrocardiogram, GLS; global longitudinal strain, LVEF; left ventricular ejection fraction, NT pro-BNP; N-terminal pro-brain natriuretic peptide, TTE; transthoracic echocardiography.

sitivity for detecting ultrastructural LV remodelling.[7] GLS is influenced by haemodynamics, blood pressure and loading conditions.[6,7,8,10,11] Relative reduction of GLS by 15% is significant, and should prompt CPT.[12]
Biomarkers may identify new cardiomyocyte damage (troponin) or myocardial wall stress (natriuretic peptides), and may raise alertness to impending toxicity, but are aspecific: baseline values are necessary for comparison and the differential diagnosis of increased values is very large.[6,7,9]
Cancer treatment alterations should not be made solely on abnormal GLS or biomarkers, but rather prompt initiation of CPT and early re-evaluation (3-4 weeks).[7,8,9]

SPECIFIC SITUATIONS

Arterial hypertension (AHT) on TKI or angiogenesis-inhibitors

After initiation of TKI or angiogenesis-inhibitors, AHT is the most frequently reported 'cardiotoxicity' (occurring in 11% to 45% of patients).[6] From a cardiological point of view, AHT grade 1 is defined as 140-159/90-99 mmHg, grade 2 as 160-179/100-109 mmHg and grade 3 as >180/>110 mmHg ('hypertensive urgency'). According to Common Terminology of Criteria for Adverse Events (CTCAE) grading, 'high-normal' blood pressures (120-139/80-89 mmHg) are considered grade 1 toxicity, AHT grade 1 corresponds to CTCAE grade 2 toxicity, AHT grade 2 corresponds to CTCAE grade 3 toxicity, and AHT grade 3 corresponds to CTCAE grade 4 toxicity. Early identification and treatment is required, aiming at reducing the risk of related morbidities (ischaemia, LVD and arterial thrombosis), targeting values <140/90 mmHg according to current European Society of Cardiology guidelines.[6,13,14]
Pain- or anxiety-induced AHT, and other contributing factors (obstructive sleep apnoea, corticosteroid treatment, use of non-steroidal anti-inflammatory drugs, *etc.*) should be handled.[6,15] Blood pressure measurement should be performed regularly during the first cycle of angiogenesis-inhibitors.[6,14,15] Once stable values are obtained, measurement intervals may be longer (2-3 weeks).[14,15]
First-line treatment includes ACEi (*e.g.* lisinopril 5 to 20 mg once daily) or sartans (*e.g.* candesartan 8 to 32 mg once daily),

TABLE 3. Overview of consultable online resources in cardio-oncology (chronologically, in order of publication).[5,6,7,8,9,10,23]

Topic		
Specialised working group	**Published**	**Reference**
Expert consensus for multimodality imaging evaluation of cardiovascular complications of radiotherapy in adults		
EACVI / American Society of Echocardiography	2013	*Lancelotti et al.*[23]
Expert Consensus for multimodality imaging evaluation of adult patients during and after cancer therapy		
American Society of Echocardiography / EACVI	2014	*Plana et al.*[10]
Position Paper on cancer treatments and cardiovascular toxicity		
ESC / ESC Committee for Practice Guidelines	2016	*Zamorano et al.*[6]
Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations		
European Society of Medical Oncology	2020	*Curigliano et al.*[7]
Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies		
Cardio-Oncology Study Group of the HFA / ICOS	2020	*Lyon et al.*[5]
Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies		
HFA / EACVI / ESC Cardio-Oncology Council	2020	*Celutkiene et al.*[8]
Role of serum biomarkers in cancer patients receiving cardiotoxic cancer therapies		
Cardio-Oncology Study Group of the HFA / ESC Cardio-Oncology Council	2020	*Pudil et al.*[9]

Formal society guidelines in the field of cardio-oncology are currently lacking: a first ESC Guidelines document is expected in 2022. Currently available resources mainly include position statements and consensus recommendations.
EACVI; European Association of Cardiovascular Imaging, ESC; European Society of Cardiology, ESMO; European Society of Medical Oncology, HFA; Heart Failure Association, ICOS; International Cardio-Oncology Society.

eventually combined with calcium-antagonists (amlodipine 5 to 10 mg once daily). Diltiazem and verapamil are contra-indicated considering cytochrome interactions.[6,7,14] Diuretics are generally avoided due to risk of electrolyte disturbances and acute kidney injury, but not formally contra-indicated.[6,7]

QTc-prolongation on TKI

TKI may cause QTc-prolongation, confirming the importance of baseline ECG : QTc > 450 ms in men and >460 ms in women prompts cardio-oncology consult.6 ECG verification should be performed after one week and at every dose increase.[6,16] When QTc prolongation >6 0ms from baseline QTc is documented, medication review should be performed, scrutinising QTc-prolonging drugs and electrolyte abnormalities.[6,16] In symptomatic QTc prolongation (dizziness, syncope, chest pain, palpitations), QTc ≥500 ms or documentation of arrhythmia, treatment should be interrupted, QTc prolonging medications must be stopped, and magnesium sulphate should be administered.[16] In these cases, telemetry monitoring is necessary until QTc normalisation.[16]

Myocarditis on immune checkpoint inhibitors

In patients undergoing treatment with immune checkpoint inhibitors (ICI), myocarditis is the most feared immune-related adverse event (irAE) because of often ambiguous clinical presentation and risk of fulminant disease course and high mortality.[17] Incidence is low but probably underestimated, and clinical presentation may be atypical.[7,17] In new-onset cardiovascular symptoms on ICI, myocarditis should be excluded.[7,17] Time of onset is early, typically within the first three months.[17] Dual ICI increases the risk, and shortens the time to onset.[17] Upon suspicion of ICI- mediated myocarditis, primary work-up includes ECG, echocardiogram, telemetry, troponin and (NT pro-)BNP dosage.[17] Cardiac MRI and/or endomyocardial biopsy may confirm the diagnosis.[17] Treatment consists of high-dose corticosteroids (1 g loading dose for three days,

KEY MESSAGES FOR CLINICAL PRACTICE

1. Baseline CV risk stratification and risk factor management is recommended in all patients undergoing potentially cardiotoxic cancer treatments: high risk patients require baseline cardio-oncological evaluation including ECG, echocardiography and biomarkers, and tailored follow-up.
2. Early diagnosis of (a-)symptomatic LVD and early HF therapy initiation increases the probability of LVEF recovery. CPT should be considered in GLS or biomarker alterations.
3. New symptoms suggesting CVD require cardiological workup and treatment.
4. Long-term cardiology follow-up should be organised at treatment completion.
5. A multidisciplinary approach is required to maximise cancer treatment completion under optimal CV surveillance.

later 1 mg/kg/d with slow tapering over one month) and interruption of ICI therapy.[7,17] Reinitiation of ICI after myocarditis in strongly discouraged.[17]

POST-TREATMENT FOLLOW-UP & LONG-TERM CANCER SURVIVORS

GENERAL MEASURES IN CANCER SURVIVORS

Despite completion of cancer treatment, long-term cardiotoxicity risk may persist until years later.[6,7] CV comorbidities coinciding with or resulting from cancer treatment require appropriate follow-up.[7] Young and paediatric cancer survivors are at particularly high risk for the development of metabolic syndrome and premature cardiovascular disease, and should be managed accordingly.[18] General measures include smoking cessation, meticulous blood pressure, lipid and glycaemic management.[6,7] Lifestyle interventions should be emphasised, including physical exercise (≥150 minutes per week).[19] Dietary measures to target weight maintenance are recommended.[20] Intentional weight loss after treatment in cancer survivors might improve prognosis and overall survival.[21]

LONG-TERM FOLLOW-UP AFTER THORACIC RADIOTHERAPY

Radiotherapy-related cardiac disease manifests years after irradiation (2-4 years for coronary artery disease, >20 years for valvular disease), with increasing risk proportional to the administered radiation dose.[8] Radiotherapy-induced valve disease usually affects left-sided heart valves, causing aortic stenosis and mitral regurgitation.[8,22] Coronary lesions usually involve left main stem and ostial stenosis.[22] In symptomatic patients, targeted yearly clinical evaluation with echocardiography and ECG is recommended, irrespective of left- or right-sided breast cancer, or mediastinal radiotherapy in other indications.[23] For asymptomatic patients, screening echocardiography commences at ten years post-radiotherapy (high-risk patients: five years) and every five years thereafter.[7,8,23]

ASYMPTOMATIC PATIENTS WITH NORMAL LVEF

Normal LVEF at therapy completion does not exclude long-term cardiotoxicity, particularly after anthracycline therapy, with potential to develop HF or LVD up to 20 years after treatment ('late-onset chronic cardiotoxicity'), with most cases occurring during the first year.[7,24] Echocardiography at treatment closure should be followed by re-evaluation at twelve months (six months in high-risk patients).[7,8] After anthracycline therapy, periodical review should be considered at a five-year interval in low- and medium-risk patients.[8] High-risk patients should undergo yearly review the first two to three years, followed by a three- to five-year interval follow-up afterwards.[8] After trastuzumab, echocardiography review should be considered at one year (low-risk), six months (medium-risk) or three months (high-risk, second review at one year).[8] If after trastuzumab, LVEF remains stable after one year, further echocardiographic follow-up is no longer required (LVEF stabilisation).[8]

PATIENTS WHO DEVELOPED LVD, SYMPTOMATIC HF OR OTHER CV TOXICITY

Early identification of LVD and early initiation of HF therapy increases the probability of LVEF recovery.[7] No data are available on how long to continue HF therapy: early discontinuation may expose the patient to adverse events.[25] General recommendation is to continue HF therapy indefinitely unless long-term stability is proven and no further cancer treat-

ment is foreseen.[7] Echocardiography should be considered at three to six months after treatment completion, further evaluation intervals depend on the type of treatment, nature of toxicity, cancer status and prognosis.[8]

CONCLUSION

Cardio-oncology is a steadily expanding subspecialty involving the entire spectrum of cardiac disease, thus stimulating intense research activity and highlighting the need for clear recommendations. The spectrum of CV toxicities associated with cancer treatments deserves specific attention.[6,7] Clinical presentations may be atypical : a high index of suspicion should be present to detect early toxicity and to initiate CPT or HF therapy. In some cases, cancer treatments should be interrupted (temporarily or permanently), and alternative treatment options discussed.[7] Currently available recommendations (*Table 3*) stem from consensus recommendations and position paper: formal cardio-oncology guidelines from the European Society of Cardiology are expected in 2022.

To maximise therapeutic success and treatment completion without, or with acceptable optimally treated, low-grade toxicity, a multidisciplinary approach is mandatory, involving oncologists, cardiologists, radiotherapists, oncological surgeons, and general practitioners.[6]

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