Echocardiography in cardio-oncology: beyond anthracyclines and HER2 receptor antagonists

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Introduction

The over-arching goal of cardio-oncology is to facilitate the effective delivery of cancer treatment while mitigating cardiovascular toxicity. This involves appropriate baseline cardiovascular risk stratification and surveillance during and after systemic anticancer therapy.[1] Surveillance recommendations are supported by an understanding of the natural history of cardiotoxicity related to specific cancer therapeutics combined with acceptable interventions to treat or mitigate cardiotoxicity.

Historically, echocardiographic surveillance has focused on patients who receive anthracycline and human epidermal growth factor receptor 2 (HER2) antagonist therapies; guidelines exist that outline the role of transthoracic echocardiography in the baseline assessment and on-going surveillance of patients receiving these therapies.[2, 3] Anthracyclines have been used since the 1970's and are effective against a wide variety of malignancies (including breast, sarcoma and haematological cancers),[4] while HER-2 antagonists first came to prominence in 1998 with evidence of the effectiveness of trastuzumab in HER-2 positive breast cancer.[5] Both of these agents can cause left ventricular (LV) dysfunction through different cellular mechanisms that ultimately culminate in the death of cardiomyocytes.[6, 7]

In recent decades there has been a huge expansion in the number of therapies available to treat cancers. More targeted agents are now available such as mitogen-activated protein kinase (MEK) inhibitors and proteosome inhibitors (PI), as well as immunotherapies such as immune checkpoint inhibitors and chimeric antigen receptor (CAR)-T cell therapy.[8] While these therapies have led to an improvement in progression-free survival and a reduction in cancer-related mortality, they are associated with a range of cardiovascular toxicities including cardiomyopathy, arrhythmias, vascular disease, systemic hypertension, pulmonary hypertension, pericardial disease and valvular heart disease.

This article focuses on the role of echocardiography beyond anthracycline and HER-2 antagonist therapy in adult patients (table 1), however most data surrounding baseline assessment and surveillance in this context is limited and derived from retrospective studies. Further research is required to establish the utility and cost-effectiveness of many of the proposed risk assessments, screening and surveillance protocols. This

	VEGFi	BRAF and MEK inhibitors	BCR-ABL inhibitors	Proteosome inhibitors	Immune checkpoint inhibitors	CAR T-cell therapy	Fluoropyrimidines	Radiotherapy
Cardiovascular complications detectable by echocardiography	• LVSD (10-20%) • Coronary thrombosis (post infarct structural and mechanical complications)	• LVSD (10%) • Coronary thrombosis	***Dasatinib:*** • Pulmonary hypertension • LVSD • Pericardial effusions	• LVSD • Coronary thrombosis • ***Carfilzomib most cardiotoxic***	• LVSD • Coronary thrombosis • Evidence of Myocarditis (LVSD, pericardial effusions)	• LVSD • Evidence of Myocarditis (LVSD, pericardial effusions)	• LVSD with RWMA secondary to coronary vasospasm or thrombosis • Takotsubo syndrome	• Valvular heart disease • LVSD and RWMA secondary to coronary artery disease • Constrictive and restrictive cardiomyopathy
Baseline echocardiography	• Recommended in those at high risk of cardiotoxicity	• Recommended in those at high risk of cardiotoxicity*	• Recommended in all patients with dasatinib use	• Recommended in all patients	• Recommended in those at high risk of cardiotoxicity	• Recommended in all patients	• Recommended in those at high risk of cardiotoxicity	• No role for routine baseline TTE
On-therapy surveillance echocardiography	• TTE every 3 months while on treatment in high-risk patient.	• TTE 4 weeks after starting treatment and every 12 weeks during treatment in high-risk patients*	• No role for surveillance • Low threshold for TTE if CV signs and symptoms develop with dasatinib use	• TTE every 3 cycles in high-risk patients	• No role for surveillance • Low threshold for TTE if CV signs and symptoms develop	• Repeat TTE 7 days after CAR T-cell infusion • TTE 1 month after infusion if cardiotoxicity or 3 months if no cardiotoxcity	• No role for surveillance • Low threshold for TTE if CV signs and symptoms develop	• No role for surveillance TTE • CV toxicity often occurs years after radiotherapy

Table 1. Overview of cancer therapies and the role of echocardiography in baseline assessment and on-therapy surveillance. All of the recommendations require further work to determine the clinical utility and cost-effectiveness of baseline assessment and on-therapy surveillance as well as the role of post-therapy surveillance. Abbreviations: VEGFi = vascular endothelial growth factor inhibitor; BRAF = rapidly accelerated fibrosarcoma B-type; MEK = mitogen-activated extracellular signal-regulated kinase; BCR-ABL = breakpoint cluster region-Abelson oncogene; CAR = chimeric antigen receptor; LVSD = left ventricular systolic dysfunction; TTE = transthoracic echocardiography; CV = cardiovascular; RWMA = regional wall motion abnormality. * Identification of cardiovascular risk using the International Cardio-Oncology Society risk stratification tool for BRAF and MEK inhibitors has been shown to perform poorly.

is particularly important in an environment where there is a growing demand for echocardiography across all aspects of cardiology. 3D echocardiography remains the preferred choice for assessment of LV ejection fraction (LVEF) and cavity dimensions in the cardio-oncology population, with no defined role for the use of contrast in routine assessment.[9]

Where chemotherapy-related cardiac dysfunction (CTRCD) is mentioned, the definition we refer to is the one outlined in the recent European Society of Cardiology (ESC) guidelines.[3] Other imaging modalities (cardiac magnetic resonance imaging, cardiac computed tomography, and nuclear imaging) play complementary roles in the diagnosis and management of cardiotoxicity following cancer therapies and interested readers can find more information in the review by Baldassarre et al.[10]

Targeted therapies

Vascular endothelial growth factor inhibitors

Vascular endothelial growth factor inhibitors (VEGFi) target pathways used by tumours to support their growth and metastasis. They are used to treat a wide variety of cancers including metastatic colorectal cancer, renal cell carcinoma, thyroid cancer and hepatocellular carcinoma.

The most common cardiotoxic effect of VEGFi is systemic hypertension (affecting 80-90% patients), however they are also implicated in de novo left ventricular systolic dysfunction (LVSD), heart failure, thrombosis, QT prolongation and arrhythmias. The incidence of LVSD with VEGFi use in real world patients (outside clinical trial settings) ranges from 10-20% with heart failure affecting 1-5%.[11] Often, the LVSD occurs in the first cycle of treatment and appears to be reversible with VEGFi dose adjustment and use of conventional heart failure therapy.[12 13]

The ESC advises that a baseline echocardiography study (within three months of the start of treatment) should be performed in patients at high risk of cardiotoxicity (as defined by the international cardio-oncology society [ICOS] risk stratification tool).[3 14] This should include 3D-LV ejection fraction (LVEF) and chamber quantification where feasible. Global longitudinal strain (GLS) should be measured, although the clinical significance of changes in GLS in the absence of significant reductions in LVEF (mild CTRCD) with VEGFi therapy is not clear and more research is required in this area.

There is an option for repeat echocardiography every three months while on treatment in high-risk patients. Alongside clinical review, echocardiography should be repeated if de-novo cardiovascular signs and symptoms occur during treatment. VEGFi use, through its associations with accelerated atherosclerosis, arterial thrombosis, and coronary vasospasm, is implicated in acute coronary syndromes. Echocardiography has a well-established role in this setting for chamber quantification, identification of regional wall motion abnormalities and screening for mechanical complications. Due to the strong association with hypertension, blood pressure should be recorded each time echocardiography is performed.[15]

Rapidly Accelerated Fibrosarcoma B-type (BRAF) and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors

BRAF and MEK inhibitors are primarily used to treat unresectable metastatic melanoma harbouring BRAF V600 gene mutations. Examples of BRAF inhibitors include dabrafenib and encorafenib and MEK inhibitors include binimetinib and cobimetinib. The range of cardiovascular toxicities associated with BRAF and MEK inhibitors include hypertension, LVSD and heart failure, atrial fibrillation, arterial and venous thrombosis, and QTc prolongation.[16]

BRAF and MEK inhibitors are often used in combination. Cardiotoxicity appears to be more common with MEK inhibitors, however the combination of both drugs enhances the risk of cardiotoxicity further.[17] Contemporary data has shown that the incidence of moderate CTRCD (new reduction in LVEF to 40-49% with a fall in LVEF of ≥10% or relative fall in GLS of ≥15%) following BRAF and MEK therapy is 10% up to 40 weeks after commencing therapy.[18] Once CTRCD has been identified there is evidence that it is reversible.[16,19] While specific recommendations for CTRCD surveillance after BRAF and MEK inhibitor therapy aren't available, Glen et al. have proposed a management pathway that includes pre-treatment echocardiography, followed by a repeat echocardiogram four weeks after starting treatment and every 12 weeks during treatment.[16] Ideally, this pathway would apply to patients at high-risk of CTRCD, however the ICOS risk stratification tool has been shown to perform poorly in identifying patients at high risk of CTRCD when applied to a real-world population of patients receiving BRAF and MEK inhibitors.[18]

Breakpoint cluster region-Abelson oncogene (BCR-ABL) inhibitors

Tyrosine kinase inhibitors (TKIs) that specifically target BCR-ABL are effective treatments for chronic myeloid leukaemia (CML). The first generation BCR-ABL TKI, imatinib, is not associated with significant cardiotoxicity, but second and third generations BCR-ABL TKIs have different cardiotoxicity profiles specific to the individual drugs.[20]

The second generation BCR-ABL TKI, dasatinib, is associated with pulmonary hypertension, LVSD and heart failure, and pericardial (and pleural) effusions, whereas nilotinib and the third generation TKI ponatinib are more strongly associated with vascular toxicity.[20] While no formal protocols exist for baseline echocardiographic assessment or surveillance with BCR-ABL TKIs, patients receiving dasatinib should have a pre-therapy echocardiogram with a low threshold for repeat assessment if signs and symptoms of CTRCD, pulmonary hypertension or pericardial effusion develop.[3]

Proteosome inhibitors

A range of different medications are approved to treat multiple myeloma in different combinations, including immunomodulatory drugs, monoclonal antibodies, alkylating agents, and proteasome inhibitors. All these drug classes are associated with cardiotoxicity, however much of the focus has been on proteosome inhibitors. These drugs exert their effect by causing proteosome instability which leads to cell cycle arrest and apoptosis.

Proteosome inhibitors are associated with a range of cardiotoxicities including hypertension, heart failure, arrhythmias, acute coronary syndrome, pulmonary hypertension and venous thrombosis.[21] Intravenously administered carfilzomib is particularly cardiotoxic and the incidence of LVSD and heart failure ranges from 4.1% - 16.2%.[22, 23] It is worth noting that patients treated for multiple myeloma tend to be ≥60 years of age and have often received anthracyclines and chest directed radiotherapy previously.[24]

Patients due to receive proteosome inhibitors should have pre-therapy echocardiography with 3D used for chamber size and function where possible. The ESC recommends surveillance for CTRCD every three cycles in high-risk patients (ICOS defined risk). This frequency of follow-up can also be considered for medium and low risk patients at the discretion of the clinical team. Measures of diastolic function should be performed because both heart failure with preserved ejection fraction and reduced ejection fraction can occur with carfilzomib.[21] As with other targeted therapies, there is a limited evidence base for the use of GLS measurement to guide clinical management with proteasome inhibitors. Another common side effect is hypertension and, as per recommendations for other targeted therapies, blood pressure should be recorded at the time of echocardiography. If CTRCD or HFPEF is identified, then treatment should follow general heart failure guidance with discontinuation of the proteosome inhibitor.[3]

Immune therapies

Immune checkpoint inhibitors

Immune-checkpoint inhibitors (ICIs) include a wide range of monoclonal antibodies targeting cytotoxic T lymphocyte-associated antigen-4 (e.g. ipilimumab), programmed death-1 (e.g. nivolumab), and programmed death-ligand 1 (e.g. atezolizumab). The targets of ICIs are expressed in cancer cells and are used by the cells to de-activate T-cells and evade the immune system. By blocking the immune checkpoint activation, ICIs activate the T-cells to kill the cancer cells. The activated T-cells also target non-cancerous tissue including the heart, which can lead to myocarditis, heart failure, LVSD (including non-inflammatory LVSD and heart failure), arrhythmias, and myocardial infarction.[25]

A complete echocardiogram is recommended in high cardiovascular risk patients prior to the initiation of ICI therapy.[3] Repeat echocardiography is indicated if the patient develops new cardiovascular signs or symptoms when treatment has been commenced, however there is no defined role for surveillance in this patient population. Echocardiography can provide useful information to aid the diagnosis of myocarditis including the identification of LVSD, regional wall motion abnormalities, new diastolic dysfunction, and pericardial effusions. It is important to note that patients with ICI-associated myocarditis may have a normal LVEF.[26] While the role of GLS is not fully defined in the setting of ICI cardiotoxicity, there is evidence that impaired GLS at the time of myocarditis diagnosis strongly associates with the development of major adverse cardiac events, regardless of whether the LVEF is impaired or not.[27] This suggests GLS may have utility in risk-stratifying these patients at time of diagnosis, however more research is needed to explore this association.

Chimeric antigen receptor T cell therapy

Chimeric antigen receptor T-cell (CAR T-cell) therapies belong to a class of drugs known as T-cell therapies, and are used to treat acute lymphoblastic leukaemia and B-cell lymphoma.[28] They are patient derived T cells that have been genetically engineered to target a tumour specific antigen, such as CD19. Most cardiotoxicity with CAR T-cell therapy occurs in the setting of cytokine release syndrome, although there is evidence to suggest certain CAR T-cells are associated with direct myocardial toxicity.[29]

Cytokine release syndrome is caused by a surge in cytokines and chemokines secondary to immune system activation, leading to a systemic inflammatory response that involves hypotension through increased vascular permeability, hypoxia and organ dysfunction. LVSD occurs in the setting of cytokine release syndrome and appears to be reversible.[30]

A full transthoracic echocardiogram with GLS measurement is recommended prior to therapy. A repeat echocardiogram is recommended seven days after CAR T-cell infusion, with a focus on LV systolic and diastolic function and any evidence of pericardial effusions.[30, 31] Echocardiography can be performed earlier if there is evidence of heart failure or high-grade cytokine release syndrome. Following treatment, repeat echocardiography is recommended at 1 month if cytotoxicity has occurred, or at 3 months if the treatment course has been uncomplicated. Although low GLS on baseline echocardiography is associated with adverse cardiac events, its utility in surveillance is unknown.[32]

Fluoropyrimidines

5-fluorouracil and its oral prodrug capecitabine are core components of chemotherapy for gastrointestinal malignancy and are used in other cancers such as advanced breast cancer. They are associated with myocardial ischaemia in up to 10% of patients (likely secondary to coronary vasospasm), hypertension, Takotsubo syndrome, acute coronary syndrome, arrhythmias and myocarditis.[33] The incidence of ischaemia is related to the dose and route of administration, with chest pain typically occurring with sudden onset following bolus 5-fluorouracil dosing and occurring in a crescendo pattern following repeated cycles of twice daily capecitabine or continuous infusion 5-fluorouracil.[34]

Echocardiography is recommended at baseline in patients with a history of symptomatic cardiovascular disease to identify pre-existing LVSD or regional wall motion abnormalities. If cardiovascular symptoms develop during treatment, echocardiography should be repeated to look for new LVSD or regional abnormalities alongside other investigations for acute coronary syndrome.[3] There is no role for echocardiography surveillance with fluoropyrimidine therapy.

Radiation therapy

Thoracic radiotherapy is associated with a variety of cardiovascular complications including pericarditis, pericardial effusions, valvular heart disease, coronary artery disease, restrictive cardiomyopathy, and conduction system disease. Often these effects manifest years after treatment. Contemporary radiotherapy techniques result in a substantially lower dose of radiation administered to the heart. The degree of cardiovascular risk relates to the dose of radiotherapy in combination with pre-existing cardiovascular risk factors, previous cardiotoxic therapies, and the time elapsed from treatment.[35]

There is no evidence to support pre-radiotherapy echocardiography and recommendations for long-term surveillance echocardiography are included in the ESC guidelines.[3] Often echocardiography is performed when patients develop signs and symptoms of heart failure and valvular heart disease after treatment. Echocardiography may detect abnormal diastolic function secondary to myocardial fibrosis with evidence of restrictive physiology, although pericardial constriction can occur concurrently with evidence of significant respiratory variation in trans-mitral and trans-tricuspid pulse-wave Doppler inflow. Valve disease often affects the mitral and aortic valves causing both stenosis and regurgitation. Evidence of radiation-induced coronary artery disease can be identified on echocardiography by the presence of new left ventricular systolic dysfunction and regional wall motion abnormalities.[35]

Assessment of thrombus and masses

Transthoracic echocardiography provides information on the location, mobility, size, haemodynamic significance, and pericardial involvement of a cardiac mass.[36] The use of ultrasound-enhancing agents can provide information on the relative vascularity of a cardiac mass which can help with diagnosis.[37] Thrombi do not have a blood supply and do not exhibit any increased perfusion relative to myocardium, benign tumours often have a poor blood supply with perfusion appearing less than the surrounding myocardium, whereas malignant tumours exhibit marked neo-angiogenesis and are highly perfused.

Conclusions

This article does not provide an exhaustive overview of the role of echocardiography in cardio-oncology outside of anthracycline and HER-2 antagonist cardiotoxicity, and there are various treatments, such as androgen deprivation therapy for prostate cancer and haematopoietic stem cell transplantation, that we have not covered. Echocardiography remains a key modality for the baseline assessment and surveillance of cardiotoxicity, however many questions remain such as the optimal surveillance strategies for cardiotoxic therapies and the clinical utility of GLS assessment in settings outside anthracycline and HER-2 antagonist cardiotoxicity.

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