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ESC 2022 Cardio-Oncology Guidelines: Paving the way for cardiovascular care through the minefield of cardiotoxicity in cancer survivorship

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Take Home Messages

- Cardiovascular disease is a prominent issue throughout cancer patients' journeys from pre-therapy to long term post-therapy surveillance
- The development of newer cancer therapies is widening the range of possible treatment related cardiovascular toxicities which require a more personalized approach to surveillance and treatment
- Thorough risk assessment and early identification throughout the cancer treatment process is important in minimizing the impact of potential long term cancer therapy-related cardiovascular toxicity.
- Data on optimal long-term surveillance for multiple therapies is still limited and requires further large extended studies to guide management as cancer survival continues to improve

Introduction

Cardiovascular disease (CVD) and cancer are two major causes of mortality worldwide (1). Chemotherapeutic agents have come a long way and the advent of targeted therapies has ushered in a new era of personalised cancer care which, along with risk factor reduction, have shown a decline in cancer mortality (2, 3). As cancer survival improves, the burden of CVD becomes more apparent (4). The Surveillance, Epidemiology and End Results (SEER) database showed that the risk of mortality from CVD was greatest in the first year of cancer diagnosis and patients diagnosed under 55 years old had a ten-fold risk of CVD related death compared to the general population (5).

Cancer therapy-related cardiovascular toxicity (CTR-CVT) is a well-established complication of chemotherapy (6). As new forms of treatment are developed, and survival improves, the short- and long-term impacts of CTR-CVT play a vital role in cancer survivorship. Guidelines have, up until now, been scarce in this area with teams being guided by expert opinion. The European Society of Cardiology (ESC) has, this year, published its first guideline on cardio-oncology, providing a comprehensive overview of CVD through the cancer patients' journey from prevention to long-term follow-up (7). This guideline, along with dedicated cardio-oncology services, will allow us to apply a more personalised approach to cancer patient care. This editorial will focus primarily on anthracycline therapies with a general overview on the more commonly encountered therapeutics (**Table 1**).

About the author

Leigh-Ann Wakefield graduated from Warwick Medical School and completed her foundation and core medical training in London. She then went on to become a cardiology registrar in the KSS deanery and has just completed ST5 training. Her main interests are in cardiac imaging and she has just started a post as an echocardiography research fellow in North West London.

Table 1. General overview of commonly used chemotherapies*

Therapy Class	Cancers Treated	Therapies	Potential Cardiovascular Effects	General monitoring Principals – Within 12 months of treatment
HER-2 therapies	Breast Cancer	Trastuzumab Pertuzumab Neratinib	HF	Baseline ECG, TTE, BNP, Troponin Repeat TTE every 3 months Consider biomarker monitoring at 3 & 12 months (Every 2-3 cycles in high-risk patients)
Endocrine Therapy	Breast Cancer	Tamoxifen Letrozole Anastrozole	HF, Metabolic syndrome, HTN, MI, VTE	Baseline CVRA (Risk estimation with SCORE2) – Then annual CVRA Regular lipid profile, BP and advice/ counselling regarding diet/exercise/smoking
Fluoropyrimidines	Gastrointestinal Breast Cancer	5-FU Capecitabine	Angina, HTN, Takotsubo, MI, myocarditis, Arrhythmia	Baseline – CVRA, ECG, lipids, HbA1c, TTE (if symptomatic) Consider baseline CAD screening in high risk
VEGF	Renal, Thyroid, Hepatocellular	Sunitinib Bevacizumab Sorafenib	HTN, Arterial and venous thrombosis, Prolong QTc, HF, MI	BP monitoring every visit, daily home monitoring for 1st cycle and after dose increases Low risk: Baseline – ECG/TTE Mod+ Risk: Baseline – ECG/TTE/BNP – Then 3-4 monthly TTE/BNP (Regular ECG if high QTc prolongation risk)
Tyrosine kinase inhibitors (BCR-ABL)	Chronic Myeloid Leukaemia	Nilotinib Dasatinib Bosutinib Ponatinib	HTN, Prolong QTc, AF, HF, Inc glucose & lipids, Effusions, Pulm HTN, MI, CVA	Baseline – CVRA/BP/ECG/HbA1c/Lipids/TTE – Then CVRA & BP every 3 months Consider ABPI/TTE/Lipids/HbA1c 3 monthly with Nilotinib, Ponatinib & Dasatinib - Each therapy in class may have unique monitoring criteria (See full guidelines for details)
Protease inhibitors	Myeloma	Bortezomib Carfilzomib	HTN, diabetes, HF, AF, MI, VTE, Pulm HTN	Baseline – CVRA/BP/ECG/TTE/BNP – Then BP every visit, BNP every cycle during first 6 cycles and TTE every 3 cycles with Carfilzomib
Androgen deprivation therapy	Prostate cancer	Goserelin Degarelix Bicalutamide Abiraterone	HTN, Diabetes, HF, MI, AF, Prolong QTc	Baseline – CVRA (Risk estimation with SCORE2)/ECG and annual CVRA Consider further ECG's if at prolonged QTc risk Consider using a GnRH class as an alternative in symptomatic pre-existing CV disease

*In-depth and unique monitoring guidelines for certain therapies can be found within the guideline. Adapted from Lyon AR *et al* (7).

AF = Atrial Fibrillation; BNP = Brain Natriuretic Peptide; CVA = Cerebrovascular Accident; CVRA = Cardiovascular Risk Assessment; ECG = Electrocardiogram; HF = Heart failure; HTN = Hypertension; MI = Myocardial infarction; TTE = Transthoracic echocardiogram; VTE = Venous Thromboembolism.

Pre-Treatment

A core Class I recommendation of the guideline is assessment of baseline risk prior to treatment but there is still a lack of data on scoring systems that can be readily applied to multiple malignancies. Although further validation is needed, risk stratification tools have been developed by the Heart Failure Association (HFA) in collaboration with the International Cardio-Oncology Society (ICOS). This categorises patients into low to very high-risk groups based on assessment of several categories (**Figure 1**) (7).

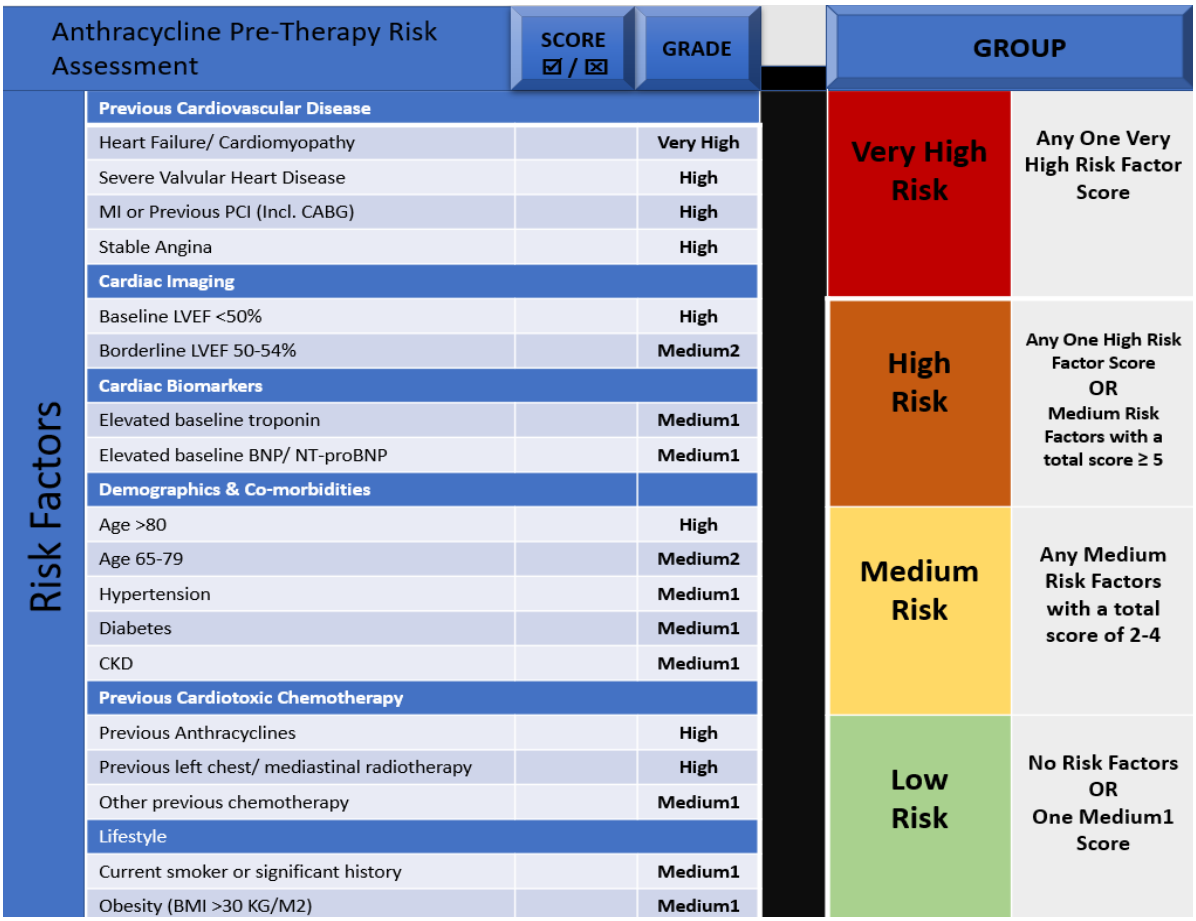

Figure 1. Example Heart Failure Association – International Cardio-Oncology Society (HFA-ICOS) pre-assessment risk tool for CVD prior to anthracycline therapy (Adapted from Lyon AR et al (7)).
CABG = Coronary Artery Bypass Graft; CKD = Chronic Kidney Disease; CVD = Cardiovascular disease; LVEF = Left Ventricular Ejection Fraction; MI = Myocardial Infarction; PCI = Percutaneous Coronary Intervention.

This creates a personalised approach to CVD prevention and surveillance allowing early identification of CTR-CVT to improve both cancer and cardiovascular outcomes.

During Treatment

Surveillance during treatment includes a 12-lead electrocardiogram, cardiac imaging and monitoring of biomarkers. The role of cardiac biomarkers is still not fully understood but one meta-analysis suggests troponin can be helpful in predicting LV dysfunction during treatment with a 69% sensitivity and a negative predictive value over 93% (8). This is especially true during anthracycline-based therapies at high-doses (8). Cardiac imaging plays a pivotal role in surveillance, especially in the form of echocardiography with global longitudinal strain, with surveillance frequency depending on patients pre-determined risk category (**Figure 2**). Early detection will enable initiation of cardioprotective therapies before, possibly irreversible, cardiac dysfunction and minimise interruptions to cancer treatment (7).

The development of any CTR-CVT should be discussed in a multi-disciplinary team setting. Cancer therapy related cardiac dysfunction (CTRCD) in the form of symptomatic or asymptomatic heart failure is the predominantly encountered CTR-CVT in anthracycline therapy (9). In symptomatic CTRCD or at least moderate asymptomatic CTRCD, guideline-based heart failure (HF) therapy is recommended. In mild asymptomatic CTRCD a beta-blocker (BB) and angiotensin-converting enzyme inhibitor (ACE-I) should be considered. Interestingly a recent systematic review and meta-analysis looking at prophylactic BB and ACE-I in anthracycline based regimes demonstrated preservation of LV function when compared with placebo (7, 10, 11). However, there was no statistical difference in occurrences of clinical HF . This could be due to small study sizes and the use of lower risk patients but could be a promising future prospect.

Figure 2. Surveillance protocol for patients receiving anthracycline-based therapy depending on risk group. Protocol starts at Pre-Treatment baseline up until 12 months post final treatment cycle (Adapted from Lyon AR et al (7)).
BIO = Cardiac Biomarkers; ECG = Electrocardiogram; ECHO = Echocardiogram.

Post-Treatment

End of successful cancer treatment is understandably a big relief for patients, but our role as cardiologists should not stop there. A large prospective study post-anthracycline therapy showed 98% of CTRCD occurred within the first year after the last anthracycline dose. (12). Response to HF therapies reduces as treatment delay increases; one study found that no patients with a treatment delay >6 months had a complete recovery of LV function (13). An end of therapy assessment should be used to determine who requires surveillance, in the first 12 months, and beyond. This depends on pre-determined risk scores, chemotherapeutic agent and events during treatment (**Figure 3**). The long-term effects of other therapies over 10 years are currently unknown with no recommendations for specific long-term surveillance unless there are other indications (7).

Very High Risk	Very high baseline risk Doxorubicin/ Equivalent ≥ 400mg/m2 RT >25 Gy MHD RT 15-25 Gy MHD + Doxorubicin ≥ 100mg/m2	Annual Cardiovascular Assessment Continuing education and optimisation of cardiovascular risk factors Cardiology referral if new symptoms develop (Class I)	Consider TTE at 1,3 and 5yrs post therapy and every 5yrs after in Adults (Class IIa)
Early High Risk (<5 years post therapy)	High baseline risk Symptomatic or asymptomatic moderate to severe CTRCD during treatment Doxorubicin 250-399 mg/m2 High risk stem cell transplant		Consider TTE every 2yrs in adults who are child and adolescent cancer survivors (Class IIa/b)
Late High Risk (>30 years post therapy)	RT >15 – 25 Gy MHD RT 5 – 15 Gy MHD + Doxorubicin ≥ 100 mg/m2 Poorly controlled cardiovascular risk factors		
Moderate Risk	Moderate baseline risk Doxorubicin 100-249 mg/m2 RT 5-15 Gy MHD RT <5 Gy MHD + Doxorubicin ≥ 100 mg/m2		Consider TTE every 5yrs in Adults and child and adolescent cancer survivors (Class IIb)
Low Risk	Low Baseline risk and normal assessment post therapy Mild CTRCD during with recovery and end of therapy RT <5 Gy MHD Doxorubicin < 100mg/m2		

Figure 3. Long Term Surveillance plan for anthracycline based chemotherapy regimes based on risk category group post treatment (Adapted from Lyon AR et al (7)).
CTRCD = Cancer therapy related cardiac dysfunction; Gy = Gray (Unit of ionizing radiation dose representing absorbed tissue dose); MHD = Mean Heart Dose; RT = Radiotherapy; TTE = Transthoracic Echocardiogram.

Conclusions

The advancing field of chemotherapeutics creates a beacon of hope for cancer patients but does open the door for an array of CTR-CVT that could impede recovery both mentally and physically. Although there is still large scope for further research, this new guideline helps us, as cardiologists, tailor a more personalised approach for patients on their journey through cancer survivorship.

Disclosures

None

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