

openheart **Cardiotoxicity: precision medicine with imprecise definitions**

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Cardiovascular diseases (CVD) and cancer are the two leading disease burdens worldwide. Epidemiological and demographic transitions, improved survival and better screening at health system level are among the factors leading to increasing overlap between these separate conditions, both in terms of aetiology and outcome. The number of cancer survivors will rise to 19 million in the USA by 2024¹ and four million in the UK by 2040.² New immune, biological and small-molecule therapies as well as existing chemotherapies alike have increased the proportion of cancer survivors for whom morbidity and mortality from CVD ('cardiotoxicity') supersedes that arising from cancer. A new medical specialty has evolved, involving multidisciplinary teams from both oncology and cardiology. Cardio-oncology recognises that *today's cancer patient is tomorrow's cardiac patient* and aims to prevent, diagnose and treat cardiotoxicity.

'Cardiotoxicity' was first coined to describe the cardiac toxicity from local anaesthetics, mercurial diuretics and digitalis in 1946. In the 1970s, the term was also used to describe the cardiac complications associated with anthracyclines (daunorubicin and doxorubicin), combination therapy (doxorubicin and radiotherapy) and for 5-fluorouracil. Early reports of 'cardiotoxicity' were predicated on the clinical syndrome of heart failure (HF), and later led to the development of a lifetime cumulative limit for anthracycline dose, although adverse cardiac effects can arise at lower doses.

There are already targeted, immune-mediated, biologically active small molecule, and monoclonal antibody therapies for over 200 recognised cancers,³ and 'precision medicine' (which uses information about a person's genes, proteins and environment to prevent, diagnose and treat disease⁴) promises further advances. Unfortunately, the same precision is currently lacking in the prediction, prognosis and treatment of cardiotoxicity and in the very definition of 'cardiotoxicity' itself. Cardio-oncology is a useful lens to study the

far-reaching implications of imprecise classifications within precision medicine for clinical practice and research.

The most widely recognised diagnosis of cardiotoxicity is based on changes in left ventricular (LV) systolic function measured by a single method, usually left ventricular ejection fraction (LVEF), sometimes on a single occasion. A fall below a certain level or an absolute change in LVEF is interpreted as an early harbinger of cardiotoxicity, but thresholds for clinical decisions vary across consensus guidelines (table 1). LVEF measurement is subject to considerable intraobserver and interobserver variability,⁵ as well as discrepancy across imaging modalities. The diagnosis of HF involves assessment and monitoring of LVEF, yet the comparison between left ventricular dysfunction in HF (which itself has problems with universality and generalisability of definitions) and cardiotoxicity has not been made, whether in terms of aetiology, epidemiology or prevention.

Cardiac dysfunction, assessed by LVEF, may be the most common manifestation of chemotherapy using anthracyclines or trastuzumab. However, limiting detection of cardiotoxicity to a single measure of LV mechanical function underestimates the clinical significance of other manifestations. For example, there is increasing evidence that, as well as structural change (eg, fall in LVEF), common anthracycline regimens trigger electrical (eg, supraventricular arrhythmia or atrial fibrillation) and biomarker (eg, rise in N-terminal pro brain natriuretic peptide or cardiac troponin) cardiotoxicity.

Advanced cancer therapies based on precision targets within the cancer kinome (the complete set of protein kinases encoded in its genome) continue to improve outcomes. However, with each novel therapy, new and often unforeseen cardiotoxicities have been reported. A broad range of cardiac sequelae are provoked by 'on-' and 'off-' target effects, including coronary artery disease,



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Table 1 Variation in definitions of cardiotoxicity across standards organisations

Standards organisation	Definition of cardiotoxicity	Comments
ASE/EACVI	LVEF fall by >10% to absolute EF <53%	Change in LV function may be global or regional (septum) Symptomatic or asymptomatic for HF
ESC	LVEF fall by >10% from baseline to EF <50%	Symptomatic or asymptomatic for HF
NCI	CTCAE HF grade 1–5	Grade 1 (asymptomatic) Grade 2 (mild to moderate symptoms) Grade 3 (symptomatic on minimal exertion or at rest) Grade 4 (life-threatening) Grade 5 (death)
CCS	LVEF fall by >10% from baseline or LVEF <53%	Guidelines also recommend (1) 3D echocardiography or same imaging modality during cancer therapy, (2) myocardial strain imaging and (3) cardiac biomarkers (N-terminal pro brain natriuretic peptide, troponin) for early detection
ESMO	Symptomatic decline in LVEF of at least 5% to <55% or asymptomatic decline in LVEF of at least 10% to <55%	Symptoms for congestive HF with signs including but not limited to S3 gallop, tachycardia or both Decline in LVEF either global or more severe in the septum

Adapted from CCS guidelines by Virani *et al* CJC 2016 (32) 831–841 and ESMO statement Curigliano *et al* Annals Oncol 2012 23 (suppl 7); vii 155–vii 166.

ASE, American Society of Echocardiography; CCS, Canadian Cardiovascular Society; CTCAE, Common Terminology Criteria for Adverse Events; EACVI, European Association of Cardiovascular Imaging; EF, ejection fraction; ESC, European Society of Cardiology; ESMO, European Society of Medical Oncology; HF, heart failure; LVEF, left ventricular ejection fraction; NCI, National Cancer Institute.

myocarditis, stress cardiomyopathy, hypertension, arterial and venous thrombosis, pulmonary hypertension and QT prolongation. However, these diverse cardiac manifestations may also be ambiguously labelled as ‘cardiotoxicity’ without adequate distinction from the aforementioned structural, electrical and biomarker subtypes.⁶ Specific

examples include coronary artery spasm and stress cardiomyopathy from fluoropyrimidines, sunitinib, bevacizumab, or rituximab; venous thromboembolism from nilotinib or thalidomide; pulmonary hypertension provoked by dasatinib; peripheral artery disease and stroke from nilotinib; hypertension from carfilzomib and sunitinib; and

Table 2 ‘Cardiotoxicity’ of common cancer therapies

	LVSD	HTN	Angina	ACS	Takotsubo	Stroke	PAD	PHTN	DVT/PE
Anthracyclines	X								
5-FU	X		X	X	X				
Gemcitabine			X	X					
Paclitaxel		X	X	X					X
Cisplatin		X	X	X		X	X		
Bleomycin			X	X		X		X	
Vincristine		X	X	X					
Cyclophos-phamide	X		X					X	
mTOR inhibitors		X	X						X
Carfilzomib	X	X		X				X	
Bevacizumab	X	X	X	X	X	X			X
Sunitinib	X	X	X	X	X	X			X
Nilotinib			X	X		X	X		X
Dasatinib	X							X	
Thalidomide									X
Rituximab		X	X	X	X				

ACS, acute coronary syndrome; DVT/PE, deep vein thrombosis/pulmonary embolism; 5-FU, 5 fluorouracil; EF, ejection fraction; HF, heart failure; HTN, hypertension; LVSD, left ventricular systolic dysfunction $\geq 2\%$ incidence as clinical HF or symptomatic or asymptomatic fall in EF >10%; mTOR, mammalian Target of Rapamycin; PAD, peripheral arterial disease; PHTN, pulmonary hypertension; Takotsubo, Takotsubo cardiomyopathy (adapted from Hermann *Circ* 2016; 133: 1272–89 and Zamorano *et al* *EJH* 2016;37: 2768).

Table 3 Examples based on proposed universal definition of cardiotoxicity

Cardiotoxicity	Timing	Demographic	Source	Affected substrate
Doxorubicin	Early	Adult	Anthracycline	Cardiomyopathy
	Late	Paediatric	Anthracycline	Cardiomyopathy
Carfilzomib	Acute	Adult	VEGF	Hypertension
PD1/PDL1	Late	Adult	Immune	Myocarditis

PD1, programmed cell death-1; PDL1, programmed death-ligand 1 VEGF, vascular endothelial growth factor.

fulminant myocarditis with immune checkpoint inhibitors (table 2.) These multiple untoward cardiovascular toxicities can be explained mechanistically by receptor interactions within the cardiac and cancer kinome.⁷ Thus, an expanding arsenal of anticancer treatments necessitates a more precise definition of cardiotoxicity.

Beyond diagnosis or cardiotoxicity, prognosis and risk prediction also present obstacles due to the variable course of cardiotoxicity by timing (early versus late), potential reversibility, target population (eg, childhood vs adult cancer survivors), underlying cardiovascular risk and the chemotherapy regimen. The benefits from precision medicine for cancer may have unpredictable costs in the form of ‘cardiotoxicities’ and studies with long-term follow-up are required to better understand disease trajectories.

A potential solution would be a universal definition of cardiotoxicity. We propose a novel nomenclature for cardiotoxicity that classifies cardiovascular side effects into a structured taxonomy based on time course (acute or chronic, early or late), population demographic (adult or paediatric as appropriate), putative source substrate (anthracycline, proteasome and vascular endothelial growth factor) and affected cardiovascular phenotype (arrhythmogenic or cardiomyopathic cardiotoxicity). Based on this structured taxonomy, one could reliably describe and distinguish cardiotoxicity in adults or children due to anthracyclines, trastuzumab, dasatinib, carfilzomib or immunotherapy, respectively. For example, anthracycline cardiomyopathy in early adulthood and late childhood could be differentiated, as well as late HER2/neu cardiac dysfunction, pulmonary hypertension associated with dasatinib, carfilzomib-associated hypertension and programmed cell death-1 (PD1)-associated myocarditis (table 3).

The absence of consistent definitions for cardiotoxicity has implications for both clinical service delivery and research studies. In healthcare provision, there is a need for uniformity of coding for cancer and CVD across electronic health records and administrative data. Moreover, registries and audits tend to be disease group-specific. For example, in the UK, National Institute for Cardiovascular Outcomes Research audit do not hold detailed cancer data and the same is true for CVD recording in the Cancer Outcomes and Services Dataset registries. The prospect of data linkage across resources is therefore limited when studying across diseases and drugs. Defining

cardiotoxicity consistently would advance consistency of diagnostic criteria, treatment thresholds, management and treatment targets. Instead, oncologists, in collaboration with cardiologists, currently take decisions to start, temporarily suspend or permanently withhold cancer treatment on the basis of imprecise criteria for cardiotoxicity and consensus rather than evidence and precision. This situation leads to suboptimal diagnosis and management, with unknown consequences on outcomes for these patients.

In research, the lack of interoperability of definitions of cardiotoxicity across trials, observational studies and registries stifles progress in discovery science (eg, genomic and -omic studies), translational science (new therapeutic targets) and clinical science (descriptive epidemiology and trials). The universal definition of myocardial infarction illustrates how ontologies, including pathophysiology and clinical coding, can be aligned and simplified across academic and clinical practice.⁸ For cancer, survival is well-defined, thereby facilitating trials, systematic reviews and meta-analyses. ‘Big data’ (across resources, including cancer and CVD registries, routine electronic health records and biobanks with genomic information) and machine learning offer scope, traversing traditional silos to derive and use ‘evidence-based’ and ‘data-driven’ definitions for cardiotoxicity.

Cardio-oncology, as a specialty in its infancy, illustrates the progress but also the challenges facing precision medicine. The majority of obstacles to a unified definition of ‘cardiotoxicity’ are in the form of artificial boundaries across healthcare (disease-specific specialties and stages in patient pathways) and research disciplines (laboratory vs clinical vs data science). Precision medicine currently focuses within these boundary lines to identify therapeutic targets, but patients have always mandated a more holistic and dynamic approach. To advance the field of cardio-oncology, the central term ‘cardiotoxicity’ needs a definition which is structured, reliable and universally agreed by patients, health professionals and researchers. In order for precision medicine to move towards 4P medicine (predictive, preventive, personalised and participatory), collaborative approaches across cardiac specialties and cancer disciplines are necessary and facilitated in the ‘big data’ era. Precision is not possible without precision of definition and diagnosis.

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