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The development and growth of cardio-oncology or onco-cardiology

Bernard Man Yung Cheung
Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Queen Mary Hospital, mycheung@hku.hk

Chu Pak Lau
Department of Medicine, School of Clinical Medicine, The University of Hong Kong

EDITORIAL

The Development and Growth of Cardio-oncology or Onco-cardiology☆

Bernard Man Yung Cheung*, Chu Pak Lau

Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong, China

Besides infectious diseases, cardiovascular (CV) diseases and cancer are the two major causes of death. The direct and indirect relationships between CV diseases and cancer are increasingly recognised (Table 1) [1]. Firstly, they tend to be more common in older people, and there are some shared aetiologies, such as tobacco use and obesity. Secondly, there are some common pathogenetic mechanisms, such as inflammation and thrombosis. Thirdly, patients with CV diseases have a higher rate of cancer while conversely, cancer patients have a higher rate of CV diseases. This is important because as cancer survival improves with newer cancer treatments, these survivors are at risk of dying from CV diseases. Fourthly, many cancer treatments, including radiotherapy, cytotoxic chemotherapy, targeted therapy, immunotherapy and CAR-T therapy have CV adverse effects (Table 2) [2]. Since cancer is a serious and often life-threatening condition, doctors and patients accept a higher level of risk and adverse effects because of the potential benefits in extending lifespan. Thus, instead of avoiding or withdrawing a drug because of its potential or actual adverse effects, both the patient and the doctor often agree to proceed with the cancer treatment. Here, the selection of dose and frequency, and monitoring of adverse effects become important.

Table 1. Cardio-oncology syndromes [1].

1. Cancer causing CV diseases
2. Cancer treatment causing CV diseases
3. CV diseases causing a pro-oncogenic environment
4. CVD treatment and diagnostics causing a pro-oncogenic environment
5. Genetic and systemic conditions causing both cancer and CV diseases

CV = Cardiovascular.

In this issue, Lam TH et al. reported a small case series of cancer patients who received an immune checkpoint inhibitor and developed myocarditis [3]. While similar cases have been reported before, this report highlights the growing need to monitor CV and other adverse effects of these relatively new cancer drugs, and the need to accumulate experience and expertise on preventing and treating these adverse effects.

Prevention is better than cure, therefore it is preferable to recognise any cancer therapy related CV complications before they become clinically manifest, in order for the therapy to be withheld or dosages adjusted. Better still, identification of high risk phenotypic/genotypic profiles in patients may, a priori, allow precision cancer therapy prescription.

Several international guidelines [4–9] have recommended CV monitoring and therapy based on expert consensus, as randomised data are scarce. From the patients' perspective, pre-existing CV diseases will increase the susceptibility to cancer therapy related CV complications, as well as a history of prior chemotherapy or radiotherapy (Table 3). CV risk and the presence of CV risk factors should be assessed as a baseline before starting cancer treatment. The CV risk

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* Corresponding author at: Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong, China. Fax: +852 28186474.
E-mail address: mycheung@hku.hk (B.M.Y. Cheung).

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Table 2. Cardiotoxicity associated with cancer drugs [2].

Anticancer agent	Type of cardiotoxicity
Anthracyclines	
Doxorubicin	HF, Arrhythmia
Epirubicin	
Alkylating agents	
Cisplatin	VTE, HTN
Antimetabolites	
Fluorouracil	Ischaemia, Arrhythmia
Capecitabine	Ischaemia, Arrhythmia
Antimicrotubule agents	
Docetaxel	HF, LVD, Arrhythmia
Monoclonal antibodies	
Rituximab	Hypotension infusion reaction, HTN
Ofatumumab	
Alemtuzumab	
Monoclonal antibodies (HER2)	
Bevacizumab	HTN, VTE
Trastuzumab	HF
Small-molecule TKIs	
Dasatinib	ACS, HF, QT prolongation, pulmonary HT
Pazopanib	HTN, Bradyarrhythmia, HF
Ponatinib	HF, HTN, Ischaemia, ATE, VTE
Sorafenib	HTN, HF, Ischaemia
Sunitinib	HTN, HF, VTE
Ibrutinib	Atrial fibrillation, HTN, Bleeding
Erlotinib	VTE
Cetuximab	
Crizotinib	Bradyarrhythmia, QT prolongation
Immune checkpoint inhibitors	
Nivolumab	Myocarditis, Arrhythmia, LVD, SCD, Vasculitis, Pericarditis
Ipilimumab	
Pembrolizumab	
Protease inhibitors	
Bortezomib	HTN
Carfilzomib	HF, VTE, HTN, ACS
mTOR inhibitors	
Everolimus	HTN
Temsirolimus	HTN
IMiDs	
Lenalidomide	VTE
Thalidomide	
Pomalidomide	
Endocrine therapy	
Selective ER modulators	VTE, QT prolongation
• Tamoxifen	
AIs	VTE, HTN, Hyperlipidaemia
• Anastrozole	
• Letrozole	
• Exemestane	
Chimeric antigen receptor (CAR) T Cell Therapy	
Tisagenlecleucel	
Axicabtagene ciloleucel	Tachycardia, Arrhythmia, Hypotension, HTN, HF Capillary leak syndrome MI (unrelated to CAD, likely due to antigen mimicry)

ACS, acute coronary syndrome; AI, aromatase inhibitor; ATE, arterial thromboembolism; CAD, coronary artery disease; CV, cardiovascular; CVA, cerebrovascular accident; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HF, heart failure; HTN, hypertension; IMiD, immunomodulatory drug; LVD, left ventricular dysfunction; MI, myocardial infarction; mTOR, mammalian target of rapamycin; QT, corrected QT interval (preferably by Fridericia's formula); SCD, sudden cardiac death; TKI, tyrosine kinase inhibitor; VTE, venous thromboembolism.

factors that are particularly relevant are blood pressure, lipids and glucose. Apart from clinical assessment of both the CV system and other comorbidities, resting ECGs to evaluate and monitor the rhythm and QTc interval are also important. Troponin and NT-proBNP level changes are often regarded as markers

Table 3. Assessment of cancer therapy related cardiovascular complications.

Parameters	Assessment	Management
Age, CV and other medical co-morbidities	Clinical	Optimisation of co-morbidities condition and risk factor control according to guidelines
History of prior chemotherapy and radiotherapy	Information on total accumulated dose and/or site applied	Therapy selection and dose adjustment
ECG	Rhythm	Avoid electrolytes disturbance
	QTc	Monitor and therapy
Cardiac biomarkers	Troponin	Monitoring and early intervention
	NT-proBNP	
Left ventricular function	Echo e.g. LVEF, GLS	Monitoring and early intervention
	CMR	Prophylactic heart failure therapy

Abbreviation: CMR = cardiac magnetic resonance scan; CV = cardiovascular; GLS = global longitudinal strain; LVEF = left ventricle ejection fraction.

of early cardiac damage. Imaging of the left ventricular function (echocardiographic and cardiac magnetic resonance imaging scans) are often necessary. For example, a reduction in left ventricular ejection fraction (LVEF) > 10% (and to <50%) or >20% alone are considered significant CV complication. Global longitudinal strain is regarded as a more sensitive marker, and a 5% reduction is considered a significant change.

From the oncological therapy perspective, some agents are associated with more CV complication than others (Table 2) [2]. For example, anthracycline dose-dependent cardiac complications are well known to most cardiologists, with complications occurring at $\geq$ 250 mg/m^2 for doxorubicin and $\geq$600 mg/m^2 for epirubicin [8]. Similarly, HER2 inhibitors such as trastuzumab may also cause heart failure. Small-molecule tyrosine kinase inhibitors such as dasatinib used for chronic myeloid leukaemia can cause acute coronary syndrome and pulmonary hypertension. The immune checkpoint inhibitors, are implicated to cause myocarditis that carries high fatality as applied in the report [3]. A number of these drugs also cause atrial and ventricular arrhythmias [9]. Most guidelines recommend baseline CV evaluation, but there is yet no consensus on the details and frequency of CVS reassessment during ongoing therapy. As these patients are under the care of oncologists who are familiar with the side-effects of these agents, their vigilance and timely notification of cardiologists when CV complications occur are critical.

Owing to specialization within medicine, few oncologists have cardiological training and conversely, few cardiologists prescribe chemotherapy and other oncology drugs regularly. Moreover, the number of new drugs for cancer has proliferated at an unprecedented pace in the last decade, such that even oncologists have difficulty keeping up with new treatments and their usages. It is under these circumstances that in advanced countries, the discipline of oncocardiology or cardio-oncology has emerged. Cancer care has always been a multidisciplinary affair, with surgery, medicine, radiotherapy, anaesthesia (pain management) and palliative medicine as its core. It now seems timely to involve the cardiologist in this team, at least in baseline assessment, and in well-timed periodic monitoring.

Conflicts of interest

None declared.

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References

[1] de Boer RA, Aboumsallem JP, Bracun V, Leedy D, Cheng R, Patel S, et al. A new classification of cardio-oncology syndromes. Cardiooncology 2021 Jun 21;7(1):24.
[2] Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, et al., ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol 2020 Feb; 31(2):171−90.
[3] Lam TS, Wong SL, Wong CK, Kwok GW, Zhou MC, So YF, et al. From bad to worse: the clinical spectrum of immune checkpoint inhibitor myocarditis and associated 3M syndrome with concomitant myositis and myasthenia. J Hong Kong Coll Cardiol 2022 [xxxx].
[4] Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2014 Oct;15(10):1063−93.
[5] Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al., ESC Scientific Document Group. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J 2016 Sep 21;37(36):2768−801.

[6] Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al., ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017 Jul 1;28(suppl_4):iv119−42.
[7] Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, et al., ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol 2020 Feb;31(2):171−90.
[8] Fradley MG, Beckie TM, Brown SA, Cheng RK, Dent SF, Nohria A, et al. Recognition, prevention, and management of arrhythmias and autonomic disorders in cardio-oncology: a scientific statement from the American heart association. Circulation 2021 Jul 20;144(3):e41−55.
[9] Alexandre J, Cautela J, Ederhy S, Damaj GL, Salem JE, Barlesi F, et al. Cardiovascular toxicity related to cancer treatment: a pragmatic approach to the American and European cardio-oncology guidelines. J Am Heart Assoc 2020 Sep 15;9(18):e018403.