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When Cancer and Cardiovascular Disease Intersect: The Challenge and the Opportunity of Cardio-Oncology

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Cancer and cardiovascular disease (CVD) commonly coexist, with increasing evidence that long-term cancer survivors are more likely to die from CVD than the general population. Effective management of CVD and its risk factors requires identification of patients at increased risk who may benefit from early intervention and their appropriate monitoring across the disease trajectory. Improving outcomes requires new models of multidisciplinary cancer care supported by care pathways. Such pathways require a clear delineation of the roles and responsibilities of all team members and provision of appropriate enablers for their delivery. These include accessible point-of-care tools/risk calculators, patient resources, and the provision of tailored training opportunities for health care providers.

Keywords

Cardio-oncology • Models of care • Guidelines • Challenges

Introduction

Since 2021, the Clinical Oncology Society of Australia (COSA) and the Cardiac Society of Australia and New Zealand (CSANZ) have been working to develop a joint approach to address the challenge of cardiovascular disease (CVD) in cancer. Both organisations have hosted joint educational meetings, are working on facilitating access to educational resources for health care professionals, and advocating for the development of resources and support for patients. This paper, written by the members of the Cardio-Oncology Working Group of COSA and the CSANZ, outlines some of the challenges in improving CVD outcomes in people with cancer in Australia and highlights key priorities areas for improvement and ongoing development.

The Clinical Challenge

Cancer and CVD are the two leading causes of morbidity and mortality in Australia, accounting for 30% and 26% of all deaths, respectively [1,2]. Both conditions frequently co-exist because of their high background prevalence, but, additionally, each condition increases the risk for the development of the other. Long-term cancer survivors are 40% more likely to die from CVD than the general population, making CVD the second leading cause of death in people with cancer [3,4]. Conversely, patients with CVD have a higher risk of developing cancer compared with the general population [5]. This co-existence and interaction between these two conditions present health care providers and the health system with significant challenges as well as opportunities.

There are more than 1.2 million cancer survivors in Australia [1] and this number is set to rise with improvements in the detection and treatment of many cancers in both adults and children [6–8]. The increased risk of CVD mortality in this patient population is observed across all cancer types, as a result of both cardiotoxic treatments (including systemic therapies and radiotherapy [9]) and shared risk factors (e.g., hypertension, smoking, obesity, diabetes mellitus, dyslipidaemia and diet), as well as common pathophysiological mechanisms (e.g., inflammation and mitochondrial dysfunction) in cancer and CVD [10–12].

Whilst the relatively rare phenomenon of overt heart failure is a well-recognised side effect of some cancer treatments (e.g., anthracyclines and trastuzumab) [13], the recognition of the importance of subclinical cardiotoxicity and general cardiovascular health in cancer patients and survivors is less appreciated by both patients and healthcare providers [14,15]. With novel cancer treatments, new cardiovascular (CV) toxicities are emerging including: accelerated atherosclerosis; arterial and venous thromboembolism; arrhythmias; systemic and pulmonary hypertension; coronary, cerebrovascular and peripheral vascular disease; myocarditis; pericardial disease; hypertension; and, metabolic abnormalities [7]. Their prevalence and impact are often not well known as they may not be attributable to prior cancer treatment and may manifest at various timepoints both during cancer treatment and long after treatment completion, such as during the haemodynamic challenge of pregnancy.

Understanding and Estimating CVD Risk

Effective management of CVD risk and prevention of cardiotoxicities requires identification of patients at increased risk who may benefit from early intervention and their appropriate monitoring across the disease trajectory. Patient care must be individualised, balancing the benefit from cancer therapy versus the potential risk of toxicity. Identification of patients at high risk of cardiovascular toxicity forms a key component of individualised care (Table 1). While for patients with high likelihood of cancer progression and recurrence, CVD may never come to realisation, cardiovascular toxicity may be a significant risk and competing cause of morbidity and mortality for those with highly curable cancers with expected longer life expectancy.

The Implementation Challenge

Many international consensus recommendations and position papers have been published relating to cardiovascular monitoring and management following cancer treatments (Table 2) [8,13,16,18–20,23]. Although key aspects of care are generally agreed upon, there remain discrepancies in these recommendations with variable physician adherence [14]. Additionally, many reviews provide very broad

Table 1 Identification of the ‘high risk’ patient—this requires every person with cancer to undergo a CV risk assessment prior to cancer treatment.*

Patients at high risk of cardiotoxicity include:

1. Patients with cancer and coexistent cardiovascular risk factors (increasing age, smoking, diabetes mellitus, hypertension, dyslipidaemia, chronic kidney disease, obesity, sedentary lifestyle).
2. Patients with established CVD (ischaemic heart disease, cardiomyopathy, heart failure, arrhythmias, peripheral or cerebrovascular disease and thromboembolism) prior to developing cancer.
3. Patients with cancer treated with potentially cardiotoxic cancer treatment, including mediastinal radiation.
4. Patients with prior exposure to potentially cardiotoxic cancer treatment.

*At the minimum, the baseline cardiovascular risk assessment should utilise either the Australian absolute cardiovascular disease risk calculator (produced by the National Vascular Disease Prevention Alliance, now part of the Australian Chronic Disease Prevention Alliance): <https://www.cvdcheck.org.au/calculator> or another similar cardiovascular risk calculator, e.g., Framingham 10 year risk calculator: <https://cvdcalculator.com/> The detailed approach to baseline cardiovascular risk stratification for cancer patients is described by Lyon et al. [16] and Lyon et al. [17].

Abbreviations: CV, cardiovascular; CVD, cardiovascular disease.

recommendations, limiting their potential for implementation, and do not specify who could deliver care and focus on optimal (idealised) quaternary level care rather than the ‘minimum standard’ required, which is critical for addressing inequity in care. Such an approach is particularly relevant in the Australian context for providing realistic models of care, given the currently relatively limited cardio-oncology services even in major hospital centres [24], and high rurality and remoteness, which makes access to specialised services difficult.

The recent release of the first international cardio-oncology guidelines by the European Society of Cardiology in collaboration with the European Haematology Association and European Society for Therapeutic Radiology and Oncology go a long way to address many of the inconsistencies in prior review papers and position statements [17]. They provide in-depth guidance on all aspects of CV care for people living with, through and beyond cancer, from primordial prevention to long-term survivorship monitoring. These guidelines have been supported by Australian clinicians across both cardiovascular and cancer fields [25]. The broad scope of these guidelines, however, makes their rapid implementation into routine care challenging, and will require local adaptations based on geographical and logistical factors. The additional recent publication of quality indicators for the provision of cardiovascular care for people living with, through and beyond cancer by the European Society of Cardiology [22] assists us to a degree, by focussing initial efforts of care in key domains deemed most critical for these patients, while a patient information booklet [26], accompanying the guidelines, explains key concepts of cardio-oncology, and empowers patients to actively participate in the decision-making process and providing them with information on the ways you can look after their CV health during treatment.

Integrating Care

Traditional fragmented models of care, in which cardiologists and oncologists operate in isolation, where the care is

initiated only after a cardiotoxicity event, lead to inferior outcomes [27]. Optimal care requires early assessment, multidisciplinary input involving primary care providers, cancer care providers and (if required) a cardiology team, ideally with experience in cardio-oncology, with care that is integrated across settings and providers. People with cancer are already busy managing multiple treatments, and without support may not adequately prioritise the care needed for the perceived distant risk of CVD as they focus on the immediate threat of cancer. Thus, patient education and self-management support is a critical aspect of care delivery. General practitioners are, historically, variably engaged with the care of their patients during acute cancer treatment and furthermore, oncologists may not be familiar with the assessment of CVD risk factors and may not prioritise it during a busy consultation. While the referral to a specialised cardio-oncology team would address this gap, such an approach is not feasible for all at risk patients.

Improving patient outcomes in Australia will likely require a new model of multidisciplinary cancer care, that includes primary care providers as the key members of the team. Such a model should be supported by a care pathway that clarifies the roles and responsibilities of all team members and facilitates access to point-of-care tools/risk calculators, patients’ resources and decision tools, and training opportunities for health care providers. How the care is operationalised at the service level will vary between settings and the complexity of care needs. Cardiovascular disease prevention may be less of a priority for patients with advanced incurable cancer at the end-of-life. On the other hand, for cancer patients and cancer survivors without CV risk factors who undergo cancer treatment that is not cardiotoxic, the appropriate management may simply involve health promotion strategies focussed on healthy lifestyle, while patients with complex CV risk factors or prior CVD may require specialist cardiologist-led care, delivered with the support of the general practitioner (GP) and the cancer team.

Table 2 Recent position papers and recommendations for management of cardiac disease in patients with cancer.

Endorsing/Publishing Entities	Title	Specific Reference
Canadian Cardiovascular Society	Canadian Cardiovascular Society Guidelines for Evaluation and Management of Cardiovascular Complications of Cancer Therapy	Virani SA, et al. <i>Can J Cardiol.</i> 2016;32:831–41 [18].
European Society of Cardiology	2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines	Zamorano JL, et al. <i>Eur Heart J.</i> 2016;37:2768–801 [13].
European Society for Medical Oncology (ESMO)	Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations	Curigliano G, et al. <i>Ann Oncol.</i> 2020;31:171–90 [19].
Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology; International Cardio-Oncology Society	Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies	Lyon AR, et al. <i>Eur J Heart Fail.</i> 2020;22:1945–60 [16].
Heart Failure Association (HFA); the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC)	Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies	Čelutkienė J, et al. <i>Eur J Heart Fail.</i> 2020;22:1504–24 [8].
Cardio-Oncology Study Group of the Heart Failure Association and the Cardio-Oncology Council of the European Society of Cardiology	Role of serum biomarkers in cancer patients receiving cardiotoxic cancer therapies	Pudil R, et al. <i>Eur J Heart Fail.</i> 2020;22:1966–83 [20].
International Cardio-Oncology Society	Cardiovascular Manifestations From Therapeutic Radiation	Mitchell JD, et al. <i>J Am Coll Cardiol CardioOnc.</i> 2021;3:360–80 [21].
European Society of Cardiology, European Haematology Association, and European Society for Therapeutic Radiology and Oncology	2022 ESC Guidelines on cardio-oncology	Lyon AR, et al. <i>Eur Heart J.</i> 2022;43:4229–361 [17].
European Society of Cardiology	European Society of Cardiology quality indicators for the prevention and management of cancer therapy-related cardiovascular toxicity in cancer treatment.	Lee GA, et al. <i>Eur Heart J Qual Care Clin Outcomes.</i> 2022;9:1–7 [22].

Future Directions

Recent funding from the Australian Government (National Health and Medical Research Council [NHMRC] and Medical Research Future Fund [MRFF]) and the National Heart Foundation of Australia has supported a range of innovative research projects focussed on development of appropriate models of care with a focus on under-served populations, including in the area of cardio-oncology. The development of the Australian Cancer Plan [28] offers a further opportunity to develop a dedicated cardio-oncology care pathway for

patients with cancer in Australia. In such a dynamic landscape, joint approaches to the implementation of best clinical practice will be invaluable.

While these are very exciting developments, there is still much that needs to be done. As well as new and expanded models of care, we need access to data to improve outcomes at both the population and individual patient level, and to improve the level of evidence for interventions that are currently offered. We also need to develop new interventions to prevent, detect and manage new toxicities such as the emerging cardiovascular toxicities of immunotherapy,

improve our detection of better-known toxicities, and to understand more comprehensively the mechanisms and mitigation of such toxicities. This offers hope for the development of treatments that will not only prevent and treat cardiovascular disease in people with cancer, but that will target the progression of cancer itself. We hope that close co-operation between professional societies such as COSA and CSANZ will help us make the most of this opportunity.

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