Cardio-oncology Issues in Lymphoma Patients

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ABSTRACT Advances in Lymphoma management have resulted in significant improvements in patient outcomes over the last 50 years. Despite these developments, cardiotoxicity from lymphoma treatments remains an important cause of mortality and morbidity in this cohort of patients. We reviewed the most common cardiotoxicities associated with lymphoma treatments and their respective investigation and management strategies, including the role of cardiac pre-assessment and late effects monitoring.

IMAJ 2022; 24: 159–164

KEY WORDS: cardiology, cardiotoxicity, lymphoma, oncology, pre-assessment

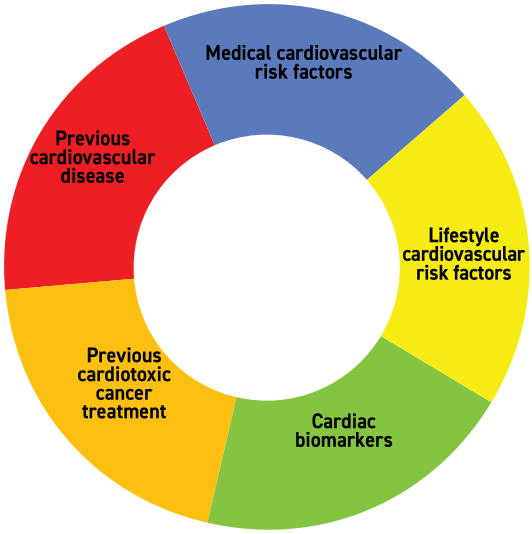
Outcomes for patients with lymphoma have improved markedly since the 1970s [1]. The 5-year relative survival for the most common subtypes range from approximately 60% for diffuse large B cell lymphoma (DLBCL) to 84–90% for classical Hodgkin's lymphoma, follicular lymphoma, chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) [2]. However, as therapies have developed and patients are living longer, we are seeing an increase in cardiovascular ill health as a direct result of some of these treatments. In a review article by Ng [3], which focused on late effects in Hodgkin lymphoma survivors between 1967 and 2007 at the Dana-Farber/Harvard Cancer Center, an increased risk of cardiovascular disease typically emerged after a latency of 10 years and remained persistently elevated over time with cardiovascular disease being the second commonest cause of death 25 years post-treatment.

The aim of this article is to outline common cardiac toxicities, identify appropriate investigation and management strategies including monitoring for late effects, and to highlight the role of cardiac pre-assessment. The discussion of lymphomas with cardiac involvement are outside the scope of this paper.

CARDIAC PRE-ASSESSMENT

In May 2020 the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society released a position statement on baseline cardiovascular risk assessment for cancer patients scheduled to receive potentially cardiotoxic therapies [4]. They identified that the treatment planning stage of cancer management provided the perfect opportunity for a comprehensive cardiovascular health assessment. This would allow the Cardio-Oncology Multi Disciplinary Team (MDT) to optimize pre-existing cardiac illness and address modifiable risk factors to reduce the potential for cardiac complications during and after treatment. This review provides a list of important cardiac risk factors and a checklist of clinical history and investigations required at baseline, see Figure 1.

Figure 1: Heart Failure Association of the European Society of Cardiology Cardio-Oncology Study Group in collaboration with the International Cardio-Oncology Society, baseline cardiovascular risk assessment checklist from Lyon et al. [4], copyright Wiley



Baseline Cardiovascular Risk Assessment Checklist

Cardiac history
Cancer treatment history
Cardiovascular risk factors

Blood pressure
HbA1c
Cholesterol profile

Cardiac troponin
B-type natriuretic peptide and N-terminal pro-BNP

Electrocardiogram

Echocardiogram

Once undertaken, the patient should be informed of the outcomes and any risks should be managed by an appropriate healthcare professional with patients being offered interventions to mitigate cardiovascular risk.

LYMPHOMA CANCER TREATMENT RELATED CARDIOTOXICITY

The common potential cardiotoxicities of lymphoma treatments are outlined by treatment modality.

Chemotherapy

Doxorubicin, an anthracycline based chemotherapy, is used to treat most subtypes of lymphoma, most commonly in the R-CHOP and ABVD regimens. Cardiotoxicity is related to total cumulative dose, and cardiomyocyte damage is caused primarily by increased reactive oxygen species and topoisomerase inhibition though other mechanisms also contribute, leading to mitochondrial dysfunction and cellular apoptosis [5]. As such, it is mainly associated with the development of left ventricular systolic dysfunction, with arrhythmias also being reported [6]. Cardiotoxicity is often classified as either early or late with the former developing within the first year of treatment and the latter more than 1 year post therapy [7]. Other anthracyclines used to treat lymphoma, although less common, include mitoxantrone (strictly, an anthracenedione) and epirubicin.

CARDIOVASCULAR DISEASE IS A COMMON CAUSE OF MORTALITY AND MORBIDITY IN LYMPHOMA PATIENTS

The mainstay of monitoring and assessment for cardiotoxicity from anthracycline chemotherapy is via a combination of cardiac imaging and biomarkers. The 2021 British Society of Echocardiography and the British Cardio-Oncology Society [8] guideline for transthoracic echocardiographic assessment of adult cancer patients receiving anthracyclines and/or trastuzumab in addition to the 2020 publication by Alexandre et al. [9] on biochemical monitoring provide a pragmatic approach to the use of these modalities [Figure 2, Figure 3].

Management of left ventricular systolic dysfunction in these patients requires urgent cardio-oncology evaluation, the initiation of an angiotensin converting enzyme inhibitor and beta blocker and usually a period of monitoring prior to treatment being recommenced/altered depending on the degree of change in left ventricular systolic function [10].

UNDERSTANDING THE CARDIOVASCULAR EFFECTS OF DIFFERENT CANCER TREATMENTS IN BOTH THE EARLY AND LATE STAGES OF THERAPY ALLOWS US TO IDENTIFY PROBLEMS PROMPTLY AND MITIGATE AGAINST SERIOUS ADVERSE EFFECTS

The prognosis of anthracycline induced cardiac dysfunction is relatively poor, with cardiovascular mortality rates ranging from 9% at 5 years and 24% at 10 years [7]. Prognosis is worse in those with symptomatic heart failure with a mortality rate of up to 60% at 2 years [7]. In a large national multicentre study, Jurczak et al. [6] demonstrated that cardiovascular death comprised one third of all mortality in lymphoma patients treated with R-CHOP. They also identified that a history of heart disease predicted cardiovascular mortality (hazard ratio [HR] 4.71, 95% confidence interval [95%CI] 3.82–6, $P < 0.001$) as did the presence of heart rhythm abnormalities related to chemotherapy (HR 4.78; 95%CI 3.63–5.92, $P = 0.01$).

Appropriate cardiac pre-assessment may help mitigate these risks as demonstrated by Dlugosz-Danecka et al. [11]. They found that a primary cardio-protection strategy in high-risk patients using ramipril and/or bisoprolol improved outcomes in non-Hodgkin lymphoma patients having doxorubicin containing regimens. With lower rates of cardiovascular death (0 vs. 14.5% at 3 years, $P < 0.05$) as well as prolonged survival (projected 5-year overall survival 74% vs. 60%, $P < 0.05$) for patients treated with primary cardio-protection.

Cardiotoxicity has also been associated with cyclophosphamide, a nitrogen mustard alkylating agent. However, this is relatively rare and primarily seen in patients receiving high doses (> 140 mg/kg) before bone marrow transplantation. Symptomatic heart failure typically develops within days of drug administration, and risk factors include total bolus dose, older age, combination therapy with other cancer drugs and mediastinal irradiation [12]. Supraventricular arrhythmias, diastolic heart failure, and hemorrhagic myocarditis [13] have also been reported. Dhesi et al. [13] suggested a strategy of detailed baseline risk assessment to identify those most vulnerable, accompanied by close monitoring of vital signs, physical examination for signs of heart failure, daily weights, an electrocardiogram, and laboratory investigations on day 2 including troponin and B-type natriuretic peptide with consideration of therapy cessation if signs of cardiotoxicity are identified.

Bruton's tyrosine kinase inhibitors

These include first-in-class ibrutinib, as well as acalabrutinib and zanutrutinib and are primarily used in the management of B cell malignancies such as mantle cell lymphoma and CLL/SLL [14]. BTK is an important molecule which plays a role in BCR, Toll-like receptor and chemokine receptor signaling which are necessary for the regulation of B cell proliferation and survival as well as adhesion, migration and tumor microenvironment forces [15]. Although most adverse effects experienced by patients taking BTKIs are mild, some can be more severe including both atrial and ventricular arrhythmias [16]. The rates of atrial fibrillation associated with ibrutinib range from 5–15% whereas the incidence of ventricular arrhythmia's are significantly lower at 596 per 100,000 person years [14], as such this section will focus on atrial fibrillation in patients taking BTKIs.

Management of BTKI associated AF provides two main challenges. First, drug-drug interactions significantly increase the risk of medication toxicities and second BTKIs are associ-

ated with an increased risk of bleeding which has implications when choosing an anticoagulation strategy.

There are a number of commonly used medications which have pharmacokinetic considerations for patients with AF using BTKIs. For example, amiodarone and rate limiting calcium channel blockers such as diltiazem and verapamil are inhibitors of CYP3A4, which subsequently increases the levels of Ibrutinib and paradoxically can exacerbate AF and also increase the risk of ibrutinib associated bleeding [17]. In addition, ibrutinib has P-glycoprotein interactions which increases the plasma levels of digoxin and subsequent risk of toxicity [17]. As such, beta blockers tend to be recommended for a rate control approach in these patients.

As with standard AF management, decisions on anticoagulation are made based on consideration of stroke and bleeding risk, with scoring systems such as CHA_2DS_2-VASc and HAS-BLED commonly used [17]. However, these scoring systems should not be used in isolation and decisions need to be made on a patient to patient basis, particularly since these scoring systems do not take into account cancer specific risk factors. Regarding BTKIs, there is an increased risk of bleeding with ibrutinib due to inhibition of collagen induced platelet aggregation [17]. Most bleeding is minor; however, major bleeding has been seen in up to 7% of patients after a year [18]. Furthermore, there is an increased risk of intracerebral bleeding with concurrent ibrutinib and warfarin therapy [18].

As such, DOACs are generally recommended for anticoagulation, in particular the factor Xa inhibitors (edoxaban, rivaroxaban and apixaban) since the direct thrombin inhibitor dabigatran is associated with P-glycoprotein interactions [17]. Low molecular weight heparin can also be considered as it has a larger evidence base for use in cancer patients, whereas warfarin is generally reserved for patients previously on warfarin before initiation of ibrutinib and unable to take DOACs [17].

In the event of clinically significant major bleeding, appropriate and timely resuscitation should be undertaken. BTKIs are usually discontinued and the transfusion of blood products are guided by local hospital policy [17], after which an MDT discussion regarding ongoing treatment would be recommended.

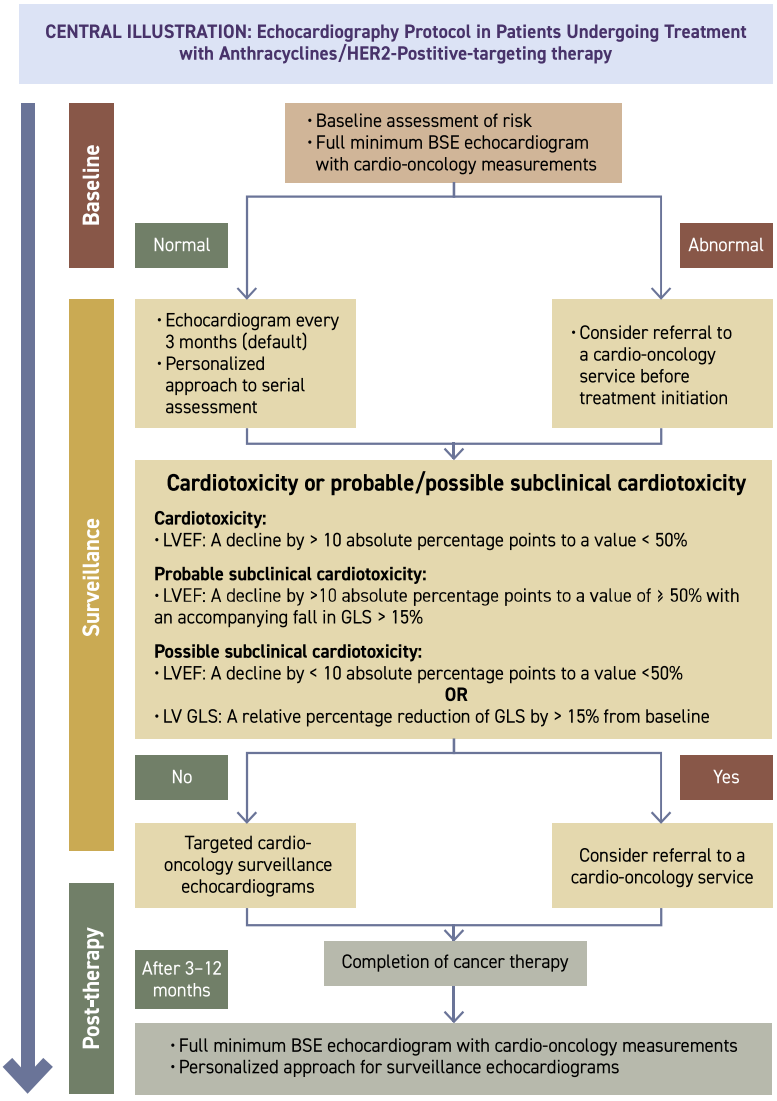
To mitigate risk, patients should undergo baseline cardiovascular risk assessment to identify those at high risk of atrial fibrillation and bleeding in order to allow for pre-treatment planning and referral to a specialist cardio-oncology service for further assessment and ongoing input [17].

Radiotherapy

Radiotherapy comprises an integral role in the management of many lymphomas, especially in Hodgkin lymphoma, where commonly patients are young with excellent outcomes. However, radiation induced heart disease is a well recognized complication of mediastinal radiotherapy [19] and remains an important cause of cardiac morbidity.

Figure 2. British Society of Echocardiography and British Cardio-Oncology Society echocardiography protocol in patients undergoing treatment with anthracyclines/HER2 positive targeted therapy from Dobson et al. [8], copyright Elsevier

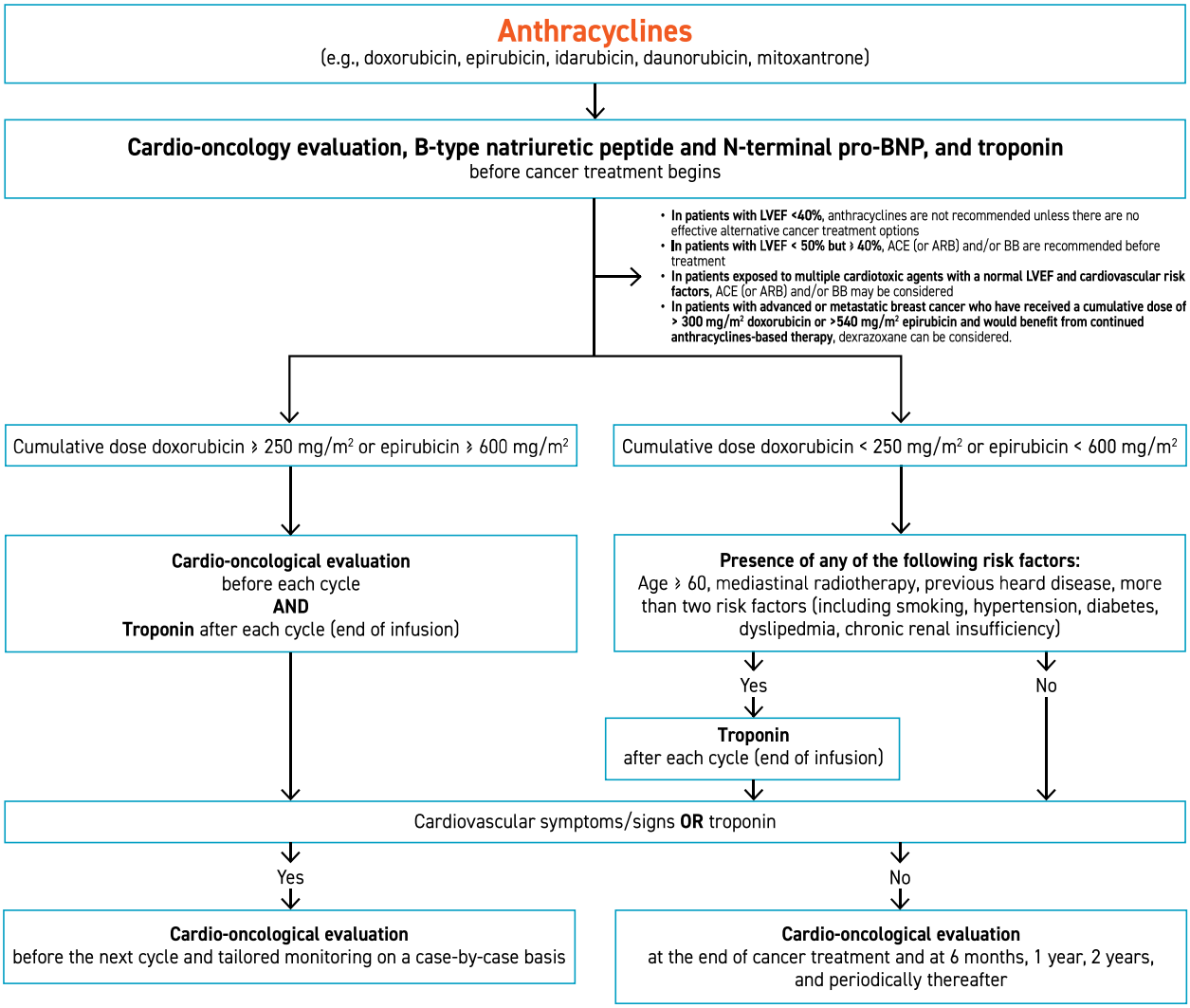
BSE = British Society of Echocardiography, LVEF = left ventricular ejection fraction, LV GLS = left ventricular global longitudinal strain



Typically, cardiotoxicity seen from childhood cancer survivors of Hodgkin's lymphoma demonstrate a variety of effects including valve disease (21% to 41%), coronary disease (17% to 23%), heart failure (8% to 17%), conduction disorders (12%) and pericardial disease (10%), exacerbated by simultaneous use of cardiotoxic systemic agents [20,21]. While concern regarding radiation cardiotoxicity is predominantly as a late effect following treatment, there is evidence that early changes may be

SCORING SYSTEMS SHOULD NOT BE USED IN ISOLATION, AND DECISIONS NEED TO BE MADE ON A PATIENT-TO-PATIENT BASIS

Figure 3. Pragmatic approach for monitoring patients treated with anthracyclines, copyright Alexandre et al. [9]



seen in the first few years [22]. Pericarditis can manifest acutely following treatment however this is uncommon and usually associated with pericardiac mediastinal tumors [23].

There is now evidence to identify several risk factors thought to increase the chances of cardiotoxicity, including total dose delivered, proximity of irradiated volume to the heart, mean heart dose and dose to individual substructures of the heart, age at treatment and additional use of cardiotoxic chemotherapy [19,23-26], in addition to the traditional cardiovascular risk factors seen at baseline.

THE USE OF SCREENING TOOLS TO HELP IDENTIFY IMPORTANT RISK FACTORS PRIOR TO TREATMENT ALLOWS FOR CARDIOVASCULAR OPTIMIZATION AND THE IDENTIFICATION OF THOSE MOST AT RISK OF COMPLICATIONS

Much of our knowledge regarding late cardiac toxicity is derived from survivors of Hodgkin's lymphoma and relates to treatment regimes and techniques used many decades ago, with large fields (such as typical Mantle radiation fields), 2-dimensional planning techniques and doses over 40Gy [21,27]. However, due, in part, to the recognition of treatment-related morbidity in these patients, consideration has been given to de-escalation of treatment to reduce these effects, whilst still maintaining excellent outcomes. As such, lower doses, smaller fields and improved radiation techniques, such as intensity modulated radiotherapy with deep inspiration breath hold have been employed, primarily to reduce unnecessary radiation to the heart and its substructures [21,28].

Early identification of risk factors is essential in the management of radiation induced heart disease. In a large retrospective

cohort study of childhood cancer survivors, Armstrong et al. [29] evaluated the relative contribution of modifiable cardiovascular risk factors on the development of major cardiac events. They found that the presence of hypertension alone significantly increased the risk for all major cardiac events among survivors exposed to both chest-directed radiotherapy and anthracyclines ($P < 0.01$). As such, the early diagnosis and appropriate management of cardiovascular risk factors may substantially reduce the development of premature cardiac disease. Furthermore, the role of follow up screening is vital to help identify problems early. While there are variations in guidelines, echocardiograms at 5-year intervals seem to be common practice, with non-invasive stress tests at 5–10 years for high risk patients [30].

A MULTIDISCIPLINARY MANAGEMENT APPROACH IS NECESSARY TO PROVIDE THE BEST POSSIBLE CARE FOR PATIENTS IN THE RAPIDLY DEVELOPING FIELD OF CARDIO-ONCOLOGY

Immune checkpoint inhibitors

Immune checkpoint inhibitors (ICI) are immunotherapeutic agents that work by binding to CTLA-4, PD-1 and PDL-1, which usually inhibit T-cell-mediated immune function, thereby helping the immune system [31]. This allows the body to attack tumor cells; however, it increases the risk of autoimmune reactions, including myocarditis. Myocarditis has an incidence rate of 1% during ICI treatment with fatality rates up to 50% in fulminant cases, particularly when associated with conduction disturbance [32]. Patient presentations are on a spectrum from breathlessness and chest pain, to shock and cardiac arrest. Echocardiographic and magnetic resonance imaging are used in the workup of these patients with myocardial biopsies considered the gold standard diagnostic test for myocarditis [33]. Clinical judgment using history and physical exam alongside biomarkers and imaging can identify those at high risk of cardiotoxicity and those deemed high risk should be evaluated by a cardio-oncologist if available [34].

Cessation of ICI treatment and treatment with high-dose glucocorticoids and subsequent immunosuppression with agents such as mycophenolate, infliximab, and intravenous immunoglobulin are commonly used [34]. In addition, standard heart failure treatment should be implemented alongside cardiorespiratory support including inotropes and vasopressors, as well as mechanical ventilation if required [33].

Chimeric antigen receptor T-cell (CAR-T) therapy

CAR-T therapy involves modifying T cells to target specific proteins on tumor cells, using a retroviral vector to transfer the engineered Chimeric Antigen Receptors (CAR) into the T cell [14]. The gene encoding the CAR allows the T cells to produce T-cell receptors specific to the required target. CAR T-cells targeting CD19 are now standard-of-care therapy in many countries for certain patients with relapsed/refractory diffuse large B-cell lymphoma and mantle cell lymphoma, with evidence of long-term outcomes significantly better than conventional chemotherapy [35,36,37].

However, cytokine release storm (CRS) is a relatively common toxicity that can result in hypotensive shock and multi-organ failure, occurring in some form in over 50% of patients and in severe form (grade 3-4) in 15–25% of patients [35-38], manifesting days to weeks following treatment. Management depends on the grade of severity, with low grade CRS being managed primarily with supportive treatments whereas fulminant presentations often require IL-6 blockade, usually with tocilizumab (steroids are used in the most severe cases) with organ support as required [39].

CONCLUSIONS

It is clear that despite great advances in survivorship from lymphoma, cardiac toxicities are an important cause of mortality and morbidity. These can exert themselves at both early and late stages and whilst there is no guarantee that we can completely avoid them there are clearly steps that can be taken to mitigate risk. Cardiac pre-assessment can play a vital part in tackling this problem and should be regularly incorporated into clinical practice.

Furthermore, the evolution of the cardio-oncologist has allowed for a more specialist approach to managing these patients, and with position papers from societies such as the British Society of Echocardiography and the International Cardio-Oncology Society, the field will continue to develop in a way that allows us to provide better evidence directed care for our patients.

Approaches to long-term follow-up remain significantly varied and given that much of the research on cardiotoxic effects in lymphoma survivors are seen in those having had treatment during childhood, it is vital that we develop clear guidance on how these patients are subsequently monitored. Certainly, the provision of developing technologies such as computed tomography coronary angiography (CTCA) for coronary disease, wearable technology for arrhythmias, and more advanced echocardiography including the use of global longitudinal strain (GLS) and 3-dimensional imaging means we are in a position to provide high quality cardio-oncology surveillance and manage later effects promptly. However, more work needs to be conducted to enhance the evidence base for the use of these technologies in order for us to appropriately streamline services and ensure that long-term screening is cost-effective and sustainable.

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All great human deeds both consume and transform their doers.
Consider an athlete, or a scientist, or an artist, or an independent business creator.
In the service of their goals they lay down time and energy and many other choices and pleasures;
in return, they become most truly themselves.

Lois McMaster Bujold (born 1949), American speculative fiction writer