Review Article

Cardio-oncology: Concepts and practice

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ABSTRACT

Substantial progress in cancer therapy increasingly allows higher cure rates, and even advanced disease can be stabilized, allowing improved survival with quality of life for months to years, meaning comorbid diseases are a growing determinant of outcome. Cardiovascular events substantially contribute to long-term morbidity and mortality in people living with or surviving cancer. In recognition of this, the subspecialty of cardio-oncology has emerged, and aims to promote cardiovascular health, whilst facilitating the most effective cancer therapy. This review describes the concept of cardio-oncology, and illustrates the role played by a specialist team in improving outcomes, using heart failure secondary to breast cancer treatment as an example. We aim to highlight pivotal original research and comprehensive summaries of the most relevant topics, providing an overview for cardiologists and oncologists about this increasingly important medical problem.

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In recent decades, remarkable progress in the detection and management of many common cancers has translated to substantial improvements in disease-free and overall survival.1,2 Even in patients with incurable cancer, contemporary therapies can often achieve medium-term and sometimes long-term disease control, requiring management strategies more akin to many other chronic diseases. Similarly, impressive reductions in cardiovascular mortality during this period mean that an increasing proportion of the population live with chronic cardiovascular diseases.3 Unsurprisingly, these secular trends have also resulted in a growing population of people with coexisting cancer and cardiovascular disease, leading to challenging management decisions that cross the boundaries of traditional medical specialties. In particular, some recently introduced cancer therapies achieve improved cancer outcomes, but with greater cardiovascular toxicity, and so require careful case-by-case consideration. In response to these concerns, the subspecialty of cardio-oncology has developed. This review not only describes the role of the cardio-oncologist, using the prevention and management of heart failure in the setting of breast cancer as a paradigm, but also discusses the background and breadth of this evolving discipline.

1. Cardiovascular risk in people with cancer

When managing cardiovascular disease in people with cancer, it is important to consider the shared origins and potential interactions of these diseases. Major cardiovascular risk
factors, such as increasing age, cigarette smoking, and obesity, are also unequivocally associated with the development of many common cancers. Therefore, by the time cancer is detected, many patients already have established or subclinical cardiovascular disease, and conversely, increasing cardiovascular disease survivorship means more people survive to develop cancer. For example, it has been shown that prior to the onset of cancer treatment, patients with colorectal cancer have reduced peak oxygen uptake during exercise, reduced heart rate variability, and reduced left ventricular ejection fraction, versus matched controls. It is also conceivable that cancer per se exacerbates cardiovascular disease, perhaps by creating a systemic proinflammatory state. Supporting this assertion, recently published data from a heterogeneous treatment naïve cancer cohort show that the concentrations of many established cardiovascular and inflammatory biomarkers rise with advancing cancer stage. It is therefore unsurprising that if a period of cancer therapy successfully achieves disease remission, future cardiovascular events may represent a substantial risk to ongoing survival and quality of life. For example, cardiovascular mortality is reported to become the principal cause of death 10 years after the diagnosis of breast cancer. Importantly, in many countries, more than 75% of women survive 10 years after a diagnosis of breast cancer, emphasizing the importance of cardiovascular disease prevention in improving their overall survival.

2. The concept of cardio-oncology

The discovery and application of anthracycline chemotherapy in the 1970s was perhaps the first event to foster partnership between oncologists and cardiologists, after it was recognized that these agents were associated with the development of heart failure. Since then, a number of other factors, including improving cancer survival and the cardiovascular toxicity of radiotherapy and molecular targeted therapies (e.g. Trastuzumab, Bevacizumab, and tyrosine kinase inhibitors), have prompted the need for increasingly formal cardiology–oncology collaborations. The concept of cardio-oncology as a subspecialty in its own right has been embraced more rapidly in some healthcare systems than others, but remains a nascent discipline in the context of clinical cardiology or oncology. The overarching aims of the cardio-oncologist are to facilitate effective cancer therapy, whilst minimizing cardiovascular sequelae, and this requires careful consideration of the risks and benefits of the treatment strategies being considered. Most often, continuing optimal cancer therapy is appropriate, whilst minimizing, and ideally preventing, interruption of cancer therapy unless it is likely that continuing will result in a net adverse outcome. Even in these circumstances, it is often possible to rapidly optimize a patient’s cardiovascular status, such that cancer therapy can safely recommence with appropriate monitoring. These potentially life-changing decisions require clear communication between a large multidisciplinary team including cardiologists, oncologists, the patient, and their family, and often require periodic reconsideration during a course of therapy. The additional complexities of considering optimal cancer care can make decision-making challenging, emphasizing the importance of understanding the mechanisms of toxicity, and benefits of cancer therapy, which requires clear communication with the oncology team. Furthermore, many decisions must be based on limited evidence, and in the context of rapidly evolving cancer therapeutics, so experience and expert opinion become increasingly important. These challenges make cardio-oncology an exciting and dynamic field, with major opportunities to improve clinical outcomes, both through organized systems of current clinical care and research programs. In spite of the complexity of individual patient circumstances, the majority of referrals to a cardio-oncology service conform a relatively small number of broad themes (Fig. 1). It is beyond the scope of this review to discuss each comprehensively, so we use the examples of heart failure prevention and management in the setting of breast cancer for the purposes of illustration. Importantly, the general principles we discuss are transferable to many other scenarios encountered by cardio-oncology teams.

3. Mechanisms of cardiac toxicity

Breast cancer is often managed with an array of highly effective, yet potentially cardiotoxic therapies. Our understanding of the mechanisms underlying this toxicity remains incomplete, although emerging studies have provided potentially important insights. Anthracycline toxicity has for many years been attributed to the myocardial oxidative stress, and recent work from Ichikawa et al. suggests this may be secondary to mitochondrial iron overload. Furthermore, they showed that Dextrazoxane, which may mitigate anthracycline cardiotoxicity in humans, is able to reduce the accumulation of iron within mitochondria. Zhang et al. have proposed anthracycline-mediated inhibition of myocardial Topoisomerase-2β as the causal mechanism, leading them to hypothesize that Topoisomerase-2α specific agents may target cancer with less cardiac toxicity. It is also possible that Dextrazoxane reduces anthracycline toxicity by interfering with their binding to Topoisomerases. It is likely that toxicity is multifactorial, with both of these mechanisms and others potentially playing a role. These studies provide hope for a mechanistic basis for strategies to reduce the cardiovascular effects of these crucial chemotherapeutic agents. Trastuzumab (or Herceptin) is another important therapeutic agent in patients with HER2 (human epidermal growth factor receptor-2, or ErbB2) overexpressing breast cancer. This monoclonal antibody binds to ErbB2, interfering with its growth and survival promoting effects in tumor cells, although when clinical trials showed an increased risk of heart failure, it became apparent that ErbB2 was also important in the myocardium. Indeed, we now recognize that cardiac epidermal growth factor receptor signaling plays an important role in the survival response to pathological stressors, although this insight has not yet resulted in the development of cancer therapies with less cardiac toxicity. It is also important to remember that the heart and wider vasculature are sensitive to the DNA-damaging effects of radiotherapy used in many breast cancer treatment regimens, nontumor tissue dose reductions represent the best means of mitigating this toxicity.
4. Natural history and epidemiology

The diverse mechanisms of chemotherapy-associated cardiac toxicity have been linked with differing clinical presentation and response to treatment, resulting in attempts to formally classify different forms. Historically, type 1 cardiotoxicity refers to a persistent and irreversible myocardial insult, as is commonly implicated in people receiving anthracyclines, whilst type 2 denotes a transient reversible deterioration in cardiac function, as has been suggested in Trastuzumab recipients. However, as with many clinical classifications, these are somewhat false distinctions, and many exceptions to these patterns are observed. For example, recent observational data suggest that normalization of anthracycline-associated left ventricular systolic dysfunction can occur after commencing appropriate heart failure therapy. Moreover, with the advent of more sensitive imaging techniques, it is now clear that many cases of Trastuzumab-related left ventricular systolic dysfunction are associated with the development of myocardial scarring.

Although it is difficult to quantify an individual patient’s risk of anthracycline-related cardiac toxicity, there is a clear association with cumulative lifetime dose. Importantly, there is no threshold dose below which these risks are absent, so potential risks and benefits must be carefully considered when planning chemotherapy. Recent data from a large heterogeneous cancer cohort (51% breast cancer) have shown that routine regimens (mean doxorubicin equivalent cumulative dose <360 mg/kg) are associated with cardiotoxicity in almost 10% of patients. Whilst this is more common than suggested by early publications on anthracycline cardiotoxicity, this to some extent reflects the routine use of serial cardiac imaging, instead of clinical evidence of heart failure, to define toxicity. Cardinale et al. also found larger cumulative anthracycline dose, lower baseline left ventricular ejection fraction (LVEF), and some cardiovascular risk factors (e.g. diabetes), to be associated with risk of cardiotoxicity. Their work also challenged the dogma, showing that most anthracycline toxicity is detectable within one year of completing chemotherapy, and that complete (11%) or partial (71%) improvement in left ventricular function commonly occurs after commencing heart failure therapy.

Whilst data describing the incidence of Trastuzumab-associated cardiac toxicity are also conflicting, it is widely accepted that concurrent use with anthracyclines substantially increases cardiotoxicity. For example, in the initial trials of concurrent therapy in women with metastatic breast cancer, the incidence of NYHA class 3 or 4 heart failure was high at 16% versus 3%. However, it is important to note that in spite of this adverse interaction, the addition of Trastuzumab remained associated with markedly improved overall survival. Based upon these data, subsequent trials in women with nonmetastatic breast cancer applied agents sequentially, with an interval between anthracycline and Trastuzumab, including an assessment of LVEF. For example, the HERA trial, which mandated 3 months separation between anthracycline and Trastuzumab, demonstrated a markedly lower incidence of clinical heart failure (0.6% vs. 0% in placebo arm) or decline in LVEF (3% vs. 0.5% in placebo arm), supporting this more cautious strategy. However, patients recruited to clinical trials are prescreened to exclude cardiovascular disease, and are at lower risk of adverse outcomes than are patients currently receiving chemotherapy; so caution should be applied in extrapolating such data to routine practice. Moreover, clinical trials tend to report adverse cardiovascular events using somewhat crude, arbitrary, and overlapping criteria that require the presence of major symptoms or declines in LVEF to be deemed high-grade toxicity. For example, the Common Terminology Criteria for Adverse Events deem major (grade 3/5) heart failure to manifest with at least NYHA class 3 breathlessness. However, a similar toxicity grading would be applied using the left ventricular systolic dysfunction criterion if a symptomatic drop in LVEF occurred. This inconsistency is a key factor in reconciling differences between clinical trials, and between trials versus
observational studies systematically recording cardiac imaging and/or biomarkers.

Radiotherapy used in the setting of breast (and other thoracic) cancer does not tend to adversely effect left ventricular systolic function in the acute phase, but may promote atherogenesis and valvular heart disease in the long-term. A meta-analysis of radiotherapy trials in this setting has supported an adverse cardiovascular risk over 15 years of follow-up, although much of the data described somewhat dated radiotherapy strategies. Indeed, other studies have failed to demonstrate this association, although the most recently published large cohort follow-up data continue to show a dose-dependent relationship between radiotherapy and increased cardiovascular risk.

5. **Assessing the risk of cardiac toxicity**

The rationale of cardiotoxicity prevention is usefully contextualized by the American Heart Association heart failure staging system, which emphasizes that symptomatic ventricular dysfunction is often an avoidable late stage in a chronic process (Fig. 2). As discussed earlier, patients with cancer frequently have other important risk factors for the development of heart failure, such as diabetes or hypertension, and these will synergize with cancer treatment-related factors to increase risk. Therefore, the first step in preventing heart failure should be a careful clinical assessment of modifiable and nonmodifiable risk factors, during a comprehensive clinical assessment. During any baseline assessment, it is also important to clarify the cancer therapy that is planned by the oncology team. Based on the earlier discussion of long-term anthracycline- and radiotherapy-associated toxicity, it is also important to carefully explore prior cancer therapy. Next, it is essential to document cardiovascular risk factors and also consider prior or ongoing manifestations of cardiovascular disease, such as angina, which may suggest progression beyond stage A of the heart failure classification. A standard cardiovascular examination should define blood pressure, features of valvular heart disease, and signs of heart failure. Routine investigations should be defined by the potential risks of the cancer therapy planned, and in the case of standard breast cancer therapy, blood tests (full blood count, renal function and electrolytes, liver function, glucose), a 12-lead ECG, and transthoracic echocardiogram are warranted. This baseline assessment provides a valuable opportunity to modify risk factors for heart failure when possible (Stage A), prevent the progression of asymptomatic structural heart disease (Stage B), and identify overt heart failure (Stage C). Patients in stage B/C, should commence neurohormonal blockade with an angiotensin-converting enzyme inhibitor and beta-blocker (discussed in detail later), then undergo reassessment to consider the risks and benefits of potentially suitable cancer therapies. This may result in selection of regimens not requiring the use of anthracyclines or Trastuzumab, but these are complex decisions requiring multidisciplinary consideration.

6. **Detection of early cardiac toxicity**

Monitoring for the development of early cardiac toxicity is a crucial component of heart failure prevention, and must be conducted on an individual patient basis, with more frequent monitoring being advisable for those at greatest perceived risk. In the context of patients with breast cancer receiving anthracyclines followed by Trastuzumab, elective reassessment is usually performed after anthracyclines, unless there is clinical suspicion of cardiovascular toxicity in the interim. Serial clinical assessment, in conjunction with cardiac imaging, and possibly circulating biomarkers, forms the basis of most guidelines, although it must be emphasized that the evidence base for these is limited and evolving. Moreover, we currently lack data from randomized-controlled trials of approaches to detect cardiac toxicity, and as discussed earlier, inconsistencies in outcome measures of heart failure or altered cardiac function hamper the comparison of observational studies.

When using the information generated from serial cardiac imaging, it is important to be aware of the limitations of this approach, which could lead to inappropriate cessation of chemotherapy, or late detection of heart failure, if overlooked. Two crucial concepts to consider are: (1) the test–retest variability of measures of cardiac function; and, (2) the

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**Fig. 2** – Heart failure staging in the context of cardio-oncology. The American Heart Association Heart Failure staging system provides a useful framework to consider the opportunities to detect and prevent chemotherapy-associated cardiotoxicity. GLS – global longitudinal strain; LVEF – left ventricular ejection fraction.
capacity of indices of cardiac function, such as LVEF, to detect early cardiac dysfunction, and the risk of heart failure. Test-retest variability, which encompasses biological variability (independent of chemotherapy) and assay variability, effectively represents the between-test variation that would be found in a control population. As this variability increases, a serial imaging approach is less able to confidently suggest that a modest change in cardiac function is genuine. For example, Simpson’s biplane assessment of LVEF using noncontrast 2-dimensional transthoracic echocardiography (2D-TTE) has an absolute test-retest variation of at least 10%.24 In other words, a drop in LVEF from 60% to 50% may be within the margin of variation, which calls in to question the value of this approach when some clinical practice guidelines recommend changes in chemotherapy if LVEF drops by 10%. The next important consideration is whether such a change in LVEF represents an early stage of cardiac toxicity, amenable to intervention, or a late manifestation of potentially irreversible damage. As imaging approaches have evolved, we now appreciate that the latter description is most accurate; indeed, people at-risk of heart failure, but with normal LVEF, frequently have detectable LV dysfunction using more sensitive approaches, such as strain imaging.25 The challenge of such increased sensitivity though is reduced specificity, and whether to intervene with cardioprotective therapies in all cases. However, it is critical that no changes to potentially life-saving chemotherapy are made based on these changes in very sensitive markers of cardiotoxicity. There is no simple solution to these challenges, but a cardio-oncology team should always be aware of them when monitoring toxicity.

Historically, multiple-gated acquisition (MUGA) radionuclide imaging formed the mainstay of cardiac monitoring in patients receiving potentially cardiotoxic therapy. Whilst it can reproducibly measure LVEF than 2D-TTE,26 and reductions during chemotherapy have been associated with adverse outcome,27,28 it may result in significant cumulative radiation exposure (≈10 mSv per study), limiting repeated imaging. Hence, as ultrasound technology has evolved, 2D-TTE has become routinely adopted in many centers, but as discussed above, this technique is much less reproducible, even in the hands of highly experienced operators.24 Whilst prechemotherapy LVEF measured by 2D-TTE has been linked with poor prognosis,29 fewer data exist regarding the prognostic relevance of changes in 2D-TTE LVEF.30 It is not clear that routine use of echo-contrast agents improves the reproducibility of LVEF measures,24 but may help in selected cases. However, it appears that 3-dimensional transthoracic echo (3D-TTE) may substantially improve test-retest variability, meaning that changes in LVEF approaching 5% can be detected.24 However, given concerns that detectable changes in LVEF may miss early cardiotoxicity, more recent studies have focused alternate indices of myocardial function. For example, one small study has used tissue Doppler imaging (TDI) to document Trastuzumab-associated reductions in peak mitral annular systolic velocity, which were detectable before LVEF declined.16 Speckle-tracking echo-derived global longitudinal strain (GLS) has demonstrated particular promise in detecting early and prognostically relevant cardiotoxicity in a recent systematic review.21 This suggested a 10–15% relative decline in GLS was the optimal cut-off, associated with sensitivity and specificity of ≈80% to detect variously defined cardiotoxicity. However, these newer techniques are yet to be tested as part of formal pathways of care, so it remains unclear that their use can improve outcome via early institution of preventative measures. Cardiac magnetic resonance imaging also offers a highly reproducible means of assessing LVEF, in addition to defining other aspects of toxicity (e.g. myocardial scarring), although availability, cost, and comfort generally limits its use as a routine monitoring tool.16,25

The technical and logistical limitations of cardiac imaging modalities have also prompted the search for effective biomarkers of early cardiac toxicity. Over a decade ago, Cardinale et al. published a large observational study of a mixed cancer cohort receiving high-dose chemotherapy, defining the value of Troponin I (TnI) measured 5 times in the 72 h after chemotherapy, and once more a month later.32 They found that TnI ≥0.08 ng/ml during the early phase (using the highest of the 5 recorded values), or at one month, was associated with deterioration in LVEF during one-year follow-up. Moreover, those with TnI ≥0.08 ng/ml on both occasions (63/703 patients) experienced very high risk of heart failure (44%), compared with those with only early TnI elevation (12%) or no TnI elevation (0.2%). However, these impressive results are challenging to apply in routine cancer care, due to the requirement of serial blood sampling during the 3 days after chemotherapy. More recently, the same authors have defined the impact of TnI ≥0.08 ng/ml in women with breast cancer receiving Trastuzumab (after chemotherapy with or without anthracyclines). Blood sampling was performed before and after every cycle of Trastuzumab, with treating clinicians being blinded to the result.33 Any elevation of TnI ≥0.08 ng/ml (occurring in 14%) was associated with a 17.6-fold increased risk of cardiac toxicity (decline in LVEF ≥10% from baseline, associated with LVEF decline to <50%) even after accounting for potential confounding factors. Most elevations of TnI were detectable by completion of the second cycle of Trastuzumab. Many other studies suggest that TnI elevation (above various thresholds) in women receiving chemotherapy for breast cancer is associated with future cardiotoxicity,34,35 although some smaller studies have failed to recapitulate this.6 Although some small studies have suggested that natriuretic peptides may also aid the prediction of early cardiotoxicity in women undergoing chemotherapy for breast cancer,37 a strong evidence base for this is currently lacking.

Other studies have introduced the concept of measuring multiple biomarkers in an attempt to refine prognostication. As discussed earlier, patients with cancer about to commence treatment exhibit higher concentrations of multiple cardiovascular biomarkers than healthy controls.6 In women with breast cancer, many of these biomarkers rise during both anthracycline and Trastuzumab therapies,38 and it is possible that the addition of myeloperoxidase to TnI may provide incremental prognostic data,35 although validation is awaited. Some groups have also asked whether biomarkers can complement cardiac imaging to define early cardiotoxicity. In 42 women receiving Trastuzumab for HER2+ breast cancer, Fallah-Rad et al. noted no change in Troponin T, high-sensitivity C-reactive protein, or brain natriuretic peptide, measured at 3 monthly intervals for one year.36 However, even at 3 months, they noted significant declines in echo
parameters, including GLS, for which a <2% absolute decline offered 92% negative predictive value for future cardiotoxicity. Sawaya et al. noted somewhat different findings in 81 women with breast cancer, assessed in the interval between anthracycline and Trastuzumab therapies.\textsuperscript{34} From a panel of advanced echo parameters and biomarkers, they found that peak systolic GLS $<-19\%$ and ultrasensitive TnI $<30$ pg/ml predicted absence of cardiotoxicity. However, in multivariate analysis, only GLS remained significantly associated with cardiotoxicity. Before meaningful conclusions can be reached regarding the value of imaging and biomarkers in this setting, randomized controlled trials with large sample sizes must be conducted.

7. Preventative therapies

The first step in preventing cardiotoxicity is to be aware of the baseline cardiovascular risk in an individual patient, along with the factors that contribute to this risk; this is an iterative process, which should continue throughout treatment. For patients with nonchemotherapy-related risk factors, such as hypertension or smoking, these should be optimized, although this requires an individualized approach. This recommendation follows expert consensus, rather than clinical trial derived evidence, but is unlikely to do harm, provided that cancer therapy is not delayed. Chemotherapy-related factors are also important in determining risk of toxicity, and the cardio-oncology team must weigh the risks of toxicity against the benefits of effective cancer control for all potentially suitable regimens. It may also be possible to reduce the risk of anthracycline-containing regimens by modifying their administration and using adjunctive therapies. For example, a recent Cochrane Collaboration systematic review and meta-analysis suggested that anthracycline cardiotoxicity is reduced by using longer infusion times, although this strategy does present logistical challenges.\textsuperscript{39}

The United States Federal Drug Administration has also approved the use of adjunctive Dexrazoxane to reduce the risk of anthracycline cardiotoxicity in women with breast cancer receiving high-dose chemotherapy.\textsuperscript{40} Whilst the mechanism of this agent’s benefit remains debated, there is reasonable evidence for its prevention of cardiotoxicity.\textsuperscript{41} Although concerns have been raised this may come at the cost of reduced anticancer efficacy, long-term follow-up of children receiving this agent has suggested no survival disadvantage or increased risk of adverse cancer outcomes.\textsuperscript{42} Emerging evidence suggests that in patients with hematologic malignancy and normal LVEF, as a result of receiving intensive chemotherapy, prophylactic use of Enalapril and Carvedilol can substantially reduce the development of heart failure or declining LVEF.\textsuperscript{43} This is also supported by meta-analysis of smaller clinical trials in patients with various cancers,\textsuperscript{41} along with a potential benefit of statins; yet, further validation is needed before this could be considered as routine management.

For patients who develop stage B or C heart failure, a different approach is clearly warranted. There is good evidence to suggest that many of these people will respond well to the standard neurohormonal blockade (with an angiotensin-converting enzyme inhibitor and beta-blocker) that would be offered to any other patient without cancer in these circumstances.\textsuperscript{15,44} Whilst these data are only from observational studies, and cannot define the prognostic benefit of this intervention, it is unlikely that randomized controlled trials of neurohormonal blockade in this secondary prevention setting would be deemed ethically justifiable. Potentially cardiotoxic chemotherapy is often halted in patients who develop significant LV dysfunction, although in those patients where LV function recovers to normal, it can be appropriate to reinitiate some therapies (e.g. Trastuzumab) with close monitoring. Importantly, recent data also indicate that many patients with chemotherapy-associated heart failure receive suboptimal cardiovascular care,\textsuperscript{45} indicating the scope of a cardio-oncology team to improve cardiovascular and cancer outcomes. It is not possible, or desirable, to be dogmatic about the circumstances where chemotherapy should stop or recommence, as decisions must carefully balance the risks of avoiding cancer treatment against further cardiac toxicity. However, whilst individualized care is important, in many cases, the opportunities to detect and prevent cardiotoxicity in patients receiving cancer therapy are broadly similar (Fig. 3). Some national guidelines exist to support such decision making in common scenarios, such as Trastuzumab cardiotoxicity,\textsuperscript{46} but it must be reemphasized that cardio-oncology teams should formulate bespoke plans in conjunction with patients.

8. Other cardio-oncology considerations

Although this review has deliberately focused on heart failure as a manifestation of cardiovascular toxicity of chemotherapy, it is important to briefly highlight other cardiovascular toxicities. Firstly, hypertension is a common problem encountered by patients receiving 'targeted therapy' with tyrosine kinase inhibitors (TKIs), or direct antagonists of growth factors, such as vascular endothelial growth factor.\textsuperscript{47} This hypertension can directly contribute to cardiac failure and other cardiovascular sequelae, and may also act as an indirect indicator of on-target toxicity (within the tumor and other tissue, such as the myocardium). Patients receiving these agents should be advised to purchase a home blood pressure monitor if possible, and keep a blood pressure diary. If not logistically possible, then they should undergo regular blood pressure monitoring at the clinic, and commence standard antihypertensive therapy if their blood pressure consistently exceeds 140/90 mmHg.\textsuperscript{48} Inadequate blood pressure control can theoretically be a justification to change cancer therapy, where risks of ongoing toxicity outweigh anticipated benefits; however, in most cases, this side effect can be well controlled over many years of therapy, and if the cancer is responding, then every effort must be made to control blood pressure. As growing numbers of patients are receiving long-term TKI therapy, it is increasingly clear that we will have to consider broader vascular and metabolic effects of these agents, which are often agent specific, and not predicted from early clinical trials.\textsuperscript{49} For example, arterial and venous thrombosis, pulmonary hypertension, diabetes, and cardiac arrhythmia have all been attributed to different targeted molecular therapies.
Finally, atrial fibrillation is recognized as an increasingly prevalent problem in cancer patients, which poses dilemmas regarding choice of anticoagulant, and how to define the risks/benefits of anticoagulation in individuals.49

9. Concluding remarks

This brief review has highlighted the increasing importance of cardiovascular disease management in people with cancer, and emphasized the important role of the cardio-oncology team in this complex and evolving process. Developing a cardio-oncology service is not a simple objective,50 and requires careful coordination with potential stakeholders and funders, but offers an important opportunity to improve clinical outcomes, and conduct valuable research. Whilst many large cardiology departments still do not have a dedicated cardio-oncology service, this is likely to become increasingly relevant subspeciality, with a pivotal role in increasing the longer-term survival and well being of many cancer sufferers.

Conflicts of interest

The authors have none to declare.

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