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Chronic cardiovascular toxicity in the older oncology patient population

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ABSTRACT

Survivorship statistics demonstrate that the incidence of cancer continues to rise worldwide, with a further 60% increase in diagnoses predicted by 2030 attributed to lifestyle risk factors, screening programmes resulting in earlier diagnosis but also the changing demographics of the population. More than a third of new cancer diagnoses and almost half of cancer survivors are now aged 70 years or older. Despite this increasing incidence, worldwide five-year cancer survival rates have improved significantly over the past two decades. After cancer, cardiovascular disease is the second most common cause of death in developed countries. With continued improvements in overall prognosis, patients with cancer have an increased exposure to cardiovascular risk factors resulting in higher cardiovascular morbidity and mortality, particularly in older patients. This relationship between cancer and cardiovascular disease is not surprising as they share the common risk factors of aging, smoking, obesity, and poor diet. In this review, we discuss the toxicity of cancer treatments on the cardiovascular system, particularly in older patients. We focus primarily on radiotherapy and anthracycline chemotherapy because of their chronic adverse effects and appraise approaches toward the detection and treatment of this toxicity to maximise survival and quality of life of older patients with cancer.

Contents

1. Introduction

Older patients with cancer present specific opportunities and risks for cancer treatment as they have high absolute risks and a high prevalence of risk factors and co-morbidity [1]. In breast cancer, where over a third of diagnoses are made in women over seventy years of age, the prevalence of cardiovascular co-morbidity and frailty is particularly high, and deaths from other causes (including cardiovascular disease) exceed breast cancer mortality [2,3]. The risks of surgery, radiotherapy,

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and chemotherapy are also increased in this population [3–6]. In multiple myeloma, where the median age at diagnosis is 75 years, there is a high prevalence of hypertension and other cardiovascular comorbidities [7], while in prostate cancer, with a peak incidence in men over the age of 75 years, the existence of cardiovascular disease directly affects treatment regimens [8]. As a direct result of this, patients with cancer over 65 years have the highest mortality rates [9], but they remain under-represented in clinical trials [10,11]. Combined with the underutilisation of cardiovascular prevention in older patients [12] this results in the underestimation of their risk of cardiovascular adverse events [10,11]. Cancer treatment can have significant 'off-target' effects on the cardiovascular system. Acute toxicity, such as dysrhythmias [13–15], hyper- and hypotension during or shortly after administration, are usually easy to identify and manage. Late effects however present a different challenge because they are irreversible and require active screening for early detection. Cardiomyopathy, pericardial disease, atrial fibrillation, vascular disease, and heart failure can all have significant impacts on quality of life and mortality. Proactive prevention, detection and treatment are required to minimise their impact on older patients with cancer.

In this review, we discuss the toxicity of cancer treatments on the cardiovascular system, particularly in older patients, and identify practical prevention and treatment strategies. We focus primarily on radiotherapy and anthracycline chemotherapy because of their chronic adverse effects, but also review other cancer treatments associated with significant cardiovascular toxicity.

2. Radiotherapy

Radiotherapy significantly reduces breast cancer recurrence in appropriate patients, but it is recognised as a cardiovascular risk factor, with mediastinal radiation of the coronary arteries and myocardium resulting in an increased risk of coronary artery stenoses and myocardial fibrosis. Even at low radiotherapy doses, endothelial function can be affected and diffuse inflammation of the coronary arteries can result in interstitial fibrosis and microvascular injury [16]. Radiotherapy regimens have changed significantly over the last 30 years, especially with the development of three-dimensional Conformal Radiation, which maximises therapy to the tumour while reducing the radiation exposure to surrounding healthy tissue. This makes it difficult to extrapolate from historical data to current regimens.

In the treatment of patients with breast cancer, myocardial exposure to ionising radiation has been shown to increase the rate of ischaemic heart disease in studies comparing the relative risks of left and right sided irradiation. Jacob et al. reported left breast treated patients experienced higher rates of coronary events compared to patients irradiated for right breast cancer, with a relative risk increase between 1.2 and 3.5 [17]. Similar conclusions were reached by Derby et al. who estimated the mean dose of cardiac radiation in left-sided breast cancer to be 6.6 Gray (Gy), compared to 2.9Gy for those with right-sided tumours. This resulted in higher rates of major coronary events in patients with left-sided (56.4%) compared to right-sided breast cancer (43.6%; $P < 0.002$). The relationship between risk of a major coronary event and mean dose of radiation to the heart was found to be linear, with the rate of coronary events increasing by 7.4% for each increase of 1Gy in mean radiation dose delivered to the heart (95% CI, 2.9 to 14.5; $P < 0.001$) [18].

Although the absolute risk of radiotherapy-induced cardiotoxicity is low in the short term, the presence of cardiac risk factors and pre-existing coronary artery disease significantly increases this risk. Most patient study cohorts include predominantly younger patients, however Doyle et al. studied women older than 65 years with stages I to III breast cancer [19]. To ensure they calculated just the effects of radiotherapy on major cardiovascular events, their methodology included statistical adjustment for cardiac risk factors and pre-existing cardiac disease. They found no significant difference in cardiac morbidity and mortality after radiotherapy for early stages of breast cancer in older patients (radiotherapy hazard ratio (HR) for myocardial infarction 0.93) [19]. However the oldest patients (>85 years) were less likely to receive radiotherapy treatment (17.3%) than patients in the 65–69 years-cohort (55.8%) [18,19]. Future studies need to include larger cohorts of older patients to inform treatment choices in this increasing large population of patients with cancer.

The European Association of Cardiovascular Imaging and the American Society of Echocardiography expert groups have provided guidelines for radiation-induced cardiotoxicity, but many of these recommendations are not supported by randomised controlled trial data and need to be interpreted in the context of absolute risk and benefit [20,21]. The recommendations include screening patients for cardiovascular risk factors prior to radiotherapy, with those at highest cardiovascular risk being considered for modified radiotherapy or an alternative treatment strategy. An alternative strategy would be to assess underlying cardiovascular risk with an established risk prediction model and then reduce that risk with evidence-based treatments such as statins or anti-hypertensive therapy [22–24].

3. Cardiotoxicity Associated with Anthracycline Treatment

Cardiotoxicities caused by cancer therapy have been well described and are recognised in both oncology and cardiology clinical practice guidelines [25,26]. Anthracycline chemotherapy remains one of the most widely used cancer treatments with proven efficacy across a wide range of solid tumours and haematological malignancies including breast cancer, sarcoma, lymphoma, and leukaemia. Despite clear anti-tumour efficacy, anthracycline therapy is recognised to result in a range of adverse cardiovascular effects [27,28]. Anthracycline cardiac toxicity ranges from subclinical myocardial injury to fulminant symptomatic left ventricular systolic failure. Toxicity is described as either acute (<1% incidence), early-onset chronic progressive (1.6–2.1% of patients) defined as during therapy and within the first year post-treatment, or late-onset chronic progressive (up to 5% incidence) which arises at least one year after chemotherapy [25,27,29]. In the case of chronic cardiovascular toxicity, this can remain undetected until decades after the first dose [27,29]. The major risk factor for anthracycline-induced chronic cardiovascular toxicity is the cumulative drug exposure [27,30]. The incidence of clinical heart failure with doxorubicin treatment rises exponentially from 5% at a cumulative dose of 400 mg/m^2 to 48% at 700 mg/m^2 [26]. Reported rates of cardiotoxicity with lower doses vary widely because of different patient populations with varying periods of follow-up, different definitions of cardiotoxicity and different screening strategies. This risk is increased in older patients or when delivered as a combination therapeutic regimen [28,31], and it is clear that cardiomyopathy can be seen many years after anthracycline treatment, even when low doses have been used [32].

There are several hypotheses for the mechanism(s) by which anthracyclines induce cardiovascular toxicity, including effects on cardiomyocyte mitochondrial function and energy balance, modulation of cellular and mitochondrial topoisomerase functionality, induction of oxidative stress with free radical formation, and impaired calcium signalling affecting myocardial relaxation [32–34]. Anthracycline-induced oxidative stress occurs through iron-mediated generation of reactive free radicals [32], resulting in markedly higher mitochondrial iron levels in cardiac tissue from patients with anthracycline-induced cardiomyopathy than other cardiomyopathies [35]. Co-administration of the iron-chelating agent dexrazoxane has been shown to decrease tissue damage, reduce the risk of left ventricular dysfunction, and the risk of cardiac failure [32,36]. Dexrazoxane is included in European and American clinical practice guidelines and treatment protocols as a cardio-protective agent for anthracycline therapy [37].

While these mechanisms can explain the acute apoptosis of cardiac myocytes seen in anthracycline toxicity, further explanation is required for the frequently long sub-clinical period seen before clinical heart

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failure is evident. In susceptible individuals, anthracycline exposure induces cardiac myocyte and progenitor cell apoptosis. In most cases, this loss of cardiac myocytes is well compensated by increase in cell volume [38] and there is no measurable reduction myocardial mass or function. However, as part of the normal aging process, over 50 million cardiac myocytes are lost each year, so over time, particularly when associated with cardiovascular stress such as the development of hypertension, decompensation, and clinical heart failure can occur. In older patients with cancer, cardiac reserve is already reduced at the point of anthracycline exposure and therefore heart failure is more common at lower anthracycline doses [1,30,38].

Age-related changes in drug pharmacokinetics also have a significant effect on the cardiotoxic effects of chemotherapy [39]. The initial blood plasma concentration of anthracyclines is higher in older patients due to a reduced rate of distribution into other body compartments, a consequence of altered regional blood flow [39]. Furthermore, an inverse correlation between age and anthracycline clearance has been described, showing a significant 9% reduction in clearance per decade age increase [39]. In addition, as anthracyclines are highly protein bound, the low serum albumin levels common in older patients, can significantly increase systemic free drug levels. Myocardial anthracycline exposure is therefore higher in older patients who then have an increased risk of drug-induced toxicity. It is important to recognise age-related differences in anthracycline effects alongside a patient's co-morbidities in the risk-benefit analysis of anthracycline treatment in older patients.

Risk factors for the development of anthracycline toxicity have been proposed - greater cumulative anthracycline dose, shorter duration of intravenous infusion, female gender, extremes of age, associated mediastinal radiotherapy, and longer duration of survival [29]. The delivery of anthracyclines as a prolonged infusion rather than a bolus has been investigated as a potential cardiovascular protection strategy [36]. Although there is evidence of reduced acute cardiac toxicity [40] long-term studies have been disappointing [41–43] and this strategy is not widely used. Liposomal formulations reduce the exposure of the cardiovascular system to anthracycline and thus reduce cardiac damage [39,40]. These formulations have equivalent efficacy to standard regimens and are used in some children in older patients but the increased cost has limited their use [44,45].

Through extrapolation of these known factors, prediction models estimating the probability of developing congestive cardiac failure, ischaemic heart disease, and stroke have been calculated [46]. By combining genetic analysis with clinical factors, Armenian et al. have established a risk prediction model which correctly identified 75% of patients in the high-risk group who went on to develop anthracycline cardiotoxicity, whereas in the low risk group 96% of patients did not develop cardiotoxicity [46]. These models are validated in survivors of childhood cancers, but accurate risk prediction for the older adult population is still being explored in order to refine cardiomyopathy surveillance and reduce anthracycline-related morbidity [47].

3.1. Detection of Anthracycline Toxicity in the Clinic: Imaging

The significant morbidity and mortality associated with chemotherapy-induced cardiovascular toxicity makes early identification and management of chemotherapeutic cardiac injury very important to improve older patients with cancer's overall survival and quality of life. Patients with early stages of cardiotoxicity are often asymptomatic, so identifying high-risk patients who are most likely to develop progressive cardiovascular disease is essential. This will require a combination of imaging studies and biomarkers to guide the timely initiation of treatment strategies [48]. Detection of cardiovascular dysfunction is most commonly achieved by serial monitoring of cardiac left ventricular ejection fraction (LVEF) using multi-gated acquisition (MUGA) or echocardiogram (ECHO), with cardiac magnetic resonance imaging (MRI) reserved for patients with suboptimal echo imaging. The International Imaging consensus and European Society of Cardiology position paper defines cardiotoxicity as a reduction in LVEF of ≥10% from baseline to a value of <50%. Although LVEF is a useful measure of load-dependent left ventricular function and has been shown to correlate with mortality, it is not equivalent to heart failure (HF), which is a clinical syndrome of symptoms and physical signs. Reduced LVEF is best characterised as a 'biomarker' associated with HF [49]. International guidelines recommend a baseline assessment of left ventricular systolic function together with global longitudinal strain to establish cardiac function prior to chemotherapy. Clinical practice recommendations for cardiotoxicity monitoring have been proposed but there is limited evidence to support the optimal timing of screening or its frequency. Curigliano et al. proposed cardiac functional screening at 6 months following anthracycline chemotherapy, annually for 2 to 3 years before continuing at 3 to 5 year intervals [25]. High risk patients, defined by anthracycline dose, extremes of age and cardiovascular risk factors, would be screened more frequently, particularly during the first 12 months after chemotherapy [25]. Because of the high costs and burden to patients, post-anthracycline screening strategies require further investigation, including cost-effectiveness analysis, before they will be widely adopted in clinical practice, particularly for older patients [11].

3.2. Detection of Anthracycline Toxicity in the Clinic: Biomarkers

One of the problems with the detection of anthracycline toxicity is that changes in myocardial function are a late sign, and may not be present until months or years after the loss of cardiac myocytes because of the heart's ability to remodel. Blood biomarkers can identify toxicity during chemotherapy therapy, allowing early cardio-protective treatment or even potentially a change in cytotoxic regimen. Cardiac troponin is released by myocyte necrosis and is both highly sensitive and specific while chronic increases in natriuretic peptides indicate ventricular wall stress so are a later and less specific indication of cardiac toxicity [50,51]. After anthracycline chemotherapy, patients with troponin-I release were shown to be at increased risk of cardiotoxicity and left ventricular systolic impairment [50]. Persistent troponin elevation a month after the last chemotherapy dose is associated with an 85% probability of a major cardiac event within 12 months. These patients can be offered appropriate early pharmacological intervention and be closely monitored. Serial negative troponin measurements identified patients at a lower risk of cardiac events (negative predictive value 99%) who may require less monitoring. Natriuretic peptides (ANP, BNP, and NT-proBNP) are released from the myocardium in response to increased wall tension and pressure overload which is associated with ventricular dysfunction [52,53]. Patients with persistently elevated NT-proBNP after chemotherapy are at increased risk of cardiac dysfunction [52–54] but low sensitivity and specificity limits its usefulness in routine clinical practice.

4. Underlying Cardiovascular Risk

In addition to addressing the specific cardiovascular risks of cancer treatment, it is important to consider underlying cardiovascular risk because coronary artery disease and stroke are the second most common cause of death in patients with cancer. Risk factors and previous cardiovascular events are very common in older people and are associated with significant morbidity and mortality [55]. A study of 100 consecutive men with localised prostate cancer at a mean age of 73 years, found that 25% had pre-existing vascular disease and an additional 74% had risk factors putting them in the high or intermediate Framingham risk categories while only 26% were receiving primary prevention treatment with statins [12]. This is particularly important as meta-analyses have shown statin treatment to reduce both prostate-specific and all-cause mortality by 24% [56,57].

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Regular exercise is known to reduce cardiovascular events and the development of co-morbidities such as diabetes mellitus, hypertension, and hyperlipidaemia. Jones et al. investigated the association between exercise and risk of cardiovascular events in adult survivors of Hodgkin's lymphoma [58]. With a median follow-up of 11.9 years, there was a 51% reduction in cardiovascular events in patients who met the American vigorous-intensity exercise guidelines (i.e. >9 metabolic equivalent hours per week) [58]. Whilst it is unrealistic to expect all older patients to attain these exercise levels, aerobic training improves myocardial contractility, diastolic relaxation and filling, increases stroke volume and attenuates pathological left ventricular remodelling [59]. Studies evaluating the benefits of 'pre-habilitation', the promotion of physical and psychological well-being from the time of diagnosis to commencing oncology treatment, have demonstrated reductions in hospital stay and improved outcomes after surgery [58]. Encouraging cancer survivors to undertake regular exercise may help to prevent or delay treatment-associated cardiovascular toxicity whilst simultaneously reducing underlying cardiovascular risk [58,59].

Particularly in older patients, high baseline cardiovascular risk significantly increases the risk of cardiotoxicity, and screening to facilitate modification of these risk factors prior to initiation of therapy is recommended to improve cardiovascular outcomes. Patients' risk can be quantified using an evidence-based score (HeartScore, QRISK-3 or 2013 ACC/AHA guideline on the assessment of cardiovascular risk) and then those at increased risk can be offered appropriate preventative lifestyle advice and treatments [60–62].

While overall cancer survival continues to improve [63,64], analysis of the Childhood Cancer Survivor Study (CCSS) has shown that fifteen to twenty-five years after diagnosis and treatment, survivors have an 8-fold increased rate of cardiac death compared age and sex matched controls (heart failure 15-fold increase, cardiovascular disease 10-fold increase, stroke 9-fold increase) [46,65]. Sibling studies have shown increased cardiovascular risk in cancer survivors - hypertension 40.2% vs. 25.5% ($p < 0.01$) and hyperlipidaemia 23.0% vs. 13.6% ($p < 0.008$) [46,66] – and that this is associated with increased cardiac mortality. Thoracic-radiation exposure is also associated with an increase in cardiovascular risk factors including obesity, dyslipidaemia, hypertension, and diabetes mellitus [67,68].

5. Conclusions

As cancer treatment has become increasingly successful at improving cancer-specific and overall survival, it has become progressively more important that cardiovascular risks are assessed and proactively managed. Early diagnosis and appropriate management of established cardiovascular risk factors such as hypertension, diabetes, dyslipidaemia, smoking and obesity are recommended for all patients with cancer and is most important in older people because of their higher absolute risk. Evidence-based interventions such as lowering blood pressure, good glycaemic control, statin therapy, smoking cessation, cardiovascular exercise, and weight reduction should be offered to all appropriate patients who should be treated in accordance with published national and international guidelines.

Many cancer treatments are associated with cardiovascular toxicity, but it is difficult to determine the magnitude of that risk for an individual patient with currently available data. The best evidence exists for anthracyclines and radiotherapy where patient and treatment related information is used in the risk-benefit analysis prior to commencing cancer treatment, in some cases selecting therapy with a lower cardiovascular toxicity profile. It is important that we use the information we have now to identify and treat each patient's underlying cardiovascular risk, and to assess the long-term cardiovascular risks associated their cancer treatment so that we can take a proactive approach to the detection and treatment of toxicity and maximise older patients' survival and quality of life.

Recommendations for reducing cardiovascular risk in older patients with cancer:
All patients should be offered appropriate lifestyle advice to reduce their cardiovascular risk in collaboration with their primary care physician:

- smoking cessation
- cardio-protective diet
- physical activity
- weight management
- alcohol consumption

Secondary Prevention
All patients with a history of established cardiovascular disease (angina, acute coronary syndromes, stroke, transient ischaemic attack or peripheral vascular disease) should undergo evidence-based investigation under the care of a specialist and be offered secondary prevention treatment as recommended in national and international guidelines.
Primary Prevention
Cancer patients without a history of a vascular event, should have their cardiovascular risk assessed using an established scoring system (QRISK®3, qrisk.org/three/; HeartScore, www.heartscore.org; JBS3, www.jbs3risk.com; or ACCC/AHA CVD risk calculator, www.cvriskcalculator.com).
Thresholds for pharmacological treatment vary between countries [60–62],but there is clinical and cost-effectiveness evidence for statin treatment using atorvastatin 20 mg daily in all patients with a 10-year cardiovascular risk of 10% or greater [61].

Conflict of Interest and Disclosure Statement

S Findlay, J Gill, and C De-Santis have no conflicts of interest to disclose.

ER Plummer has received travel expenses and honoraria for speaking at educational meetings or advisory boards from Bayer, BMS, Clovis Oncology, Genmab, MSD, Novartis, Octimet, Pierre Faber and Roche.

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Author Contributions

SG Findlay has contributed to the conception, design, writing and revising of the paper.
JH Gill has contributed to the conception, design, writing and revising of the paper.
R Plummer has contributed to the conception, design and revising of the paper.
C De-Santis has contributed to the reviewing and revising of the paper.
C Plummer has contributed to the conception, design and revising of the paper.
Each author has participated sufficiently in the work to take responsibility for all the content.

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