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Cardio-Oncology in the Older Adult

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Abstract

Heart disease and cancer are the leading causes of death in older adults. Many first-line cancer treatments have the potential for cardiotoxicity. Age-related risk factors, pre-existing cardiac disease, and a high prevalence of comorbidities are reasons for increased cardiotoxicity in older adults. Concerns regarding cardiotoxicity may lead to frailty bias and undertreatment, resulting in suboptimal outcomes. There is an urgent need for geriatric-specific evidence and guidelines to help tailor care for this vulnerable group. A multi-disciplinary approach based on close collaboration between oncologists, cardiologists, and geriatricians, among other specialist clinicians is essential.

Keywords

Cardio-oncology; geriatrics; older adult; cardiotoxicity; cardiotoxic treatments

Introduction

Cardio-oncology is an area of growing interest in recent years. Data are lacking on cardio-oncology specific to older adults. This is increasingly becoming important as advances in cancer treatments result in longer patient survival (1). The 5-year survival of patients diagnosed with cancer has steadily increased from 49% to 69% over the past three decades (1). The proportion of cancer survivors that are 65 years or older has increased exponentially. By 2020, it is estimated that the number of cancer survivors will increase by 31% to 18 million, and that two-thirds of all cancer survivors will be 65 years or older (2–4). As the incidence of cancer rises with increasing age, so does the prevalence of

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cardiovascular disease (CVD). Those older than 65 years account for more than half of CVD hospitalizations and approximately 80% of deaths (5). Even more striking, those 75 years of age or older account for 50% of cardiovascular deaths despite accounting for only 6% of the population (5).

Despite the increased prevalence of older adults living with cancer and associated treatment toxicities, patients 65 years or older are underrepresented in clinical trials (5–7). Older patients are frequently offered lower doses of chemotherapy due to concerns of toxicity, presumed frailty, and the high likelihood of coexisting comorbidities. Several observational studies have noted poorer outcomes in this group possibly due to undertreatment and age-related factors (8, 9). As a result, optimal care of older adults with cancer necessitates evidence-based and guideline-directed care specific to this vulnerable group. Such care is especially critical for elderly patients at risk for cardiotoxicity.

Risk Factors of Cardiotoxicity

The 2016 American Society of Clinical Oncology (ASCO) Clinical Practice Guideline for the prevention and monitoring of cardiac dysfunction in survivors of adult cancers identifies the following risk factors for cardiac dysfunction: older age (age greater than 60 years), high-dose anthracycline therapy, high-dose radiotherapy, cardiovascular risk factors including smoking, diabetes, dyslipidemia, and obesity, borderline low cardiac function, valvular disease, and history of myocardial infarction (10). An estimated 80% of patients 60 years of age or older have at least one comorbid condition and 50% have two or more (11). In patients older than 80 years, as many as 70% have multiple comorbid conditions (11). In a retrospective analysis of patients receiving treatment for acute myeloid leukemia, a larger proportion of patients older than 60 years had significant comorbidities compared with those younger than 60 years (58.3% vs. 26.3%) (12). Not surprisingly, these comorbidities include diabetes mellitus, chronic obstructive lung disease, chronic kidney disease, and pre-existing heart disease (12). The cumulative effect of these factors, as illustrated in Figure 1 and previously described by Shenoy et al. (13), can be described as a “snowball effect.” The “snowball,” formed of baseline age-related factors is “set in motion” by the cancer diagnosis and is further exacerbated by cancer treatments which cause direct injury to tissues and organs. Polypharmacy and use of potentially inappropriate medications are prevalent in older adults and can exacerbate the toxicity associated with cancer treatments (14–16). A multidisciplinary approach, including pharmacist involvement, is vital to preventing polypharmacy and inappropriate medication-related toxicities. Medication therapy management (MTM), consisting a thorough review of medications by a pharmacist, is increasingly being adopted in older patients and those with multiple comorbidities, including those with cancer (17). A growing number of retrospective studies indicate that MTM significantly reduces drug-drug interactions, adverse drug events, and non-adherence in older patients with cancer (17, 18).

Cancer Treatment-Specific Considerations

Comprehensive reviews exist on the cardiac toxicity of chemotherapy agents (10, 19, 20); in this article, cancer therapies with the highest risk for cardiotoxicity in the elderly population

are discussed below including anthracyclines, trastuzumab, tyrosine kinase inhibitors, fluoropyrimidines, and radiation therapy.

Anthracyclines

Anthracyclines remain the first-line therapy for many cancers including breast cancer, hematological cancers, and sarcoma. They are incorporated in more than 50% of treatment regimens for these cancers (21, 22). They are also the most commonly associated cancer drugs known to cause irreversible dose-dependent cardiotoxicity. In a meta-analysis by Smith et al., an anthracycline-based regimen was associated with a higher risk of cardiotoxicity with an odds ratio of 5.43 compared with a non-anthracycline regimen (21). Around 75% of patients with anthracycline-related left ventricular systolic dysfunction do not have full recovery to normal function (23). The incidence of heart failure has been estimated at 2% at 200mg/m², 5% at 400 mg/m², 16% at 500 mg/m², and 26% at 550 mg/m² (24, 25). ASCO guidelines estimate a 1.6 to 6.8-fold increased risk of cardiac dysfunction in elderly patients, defined as 60 years of age or older, when compared to younger patients with cancer (10). Furthermore, studies limited to patients 65 years of age or older, were noted to have increasing risk of cardiac dysfunction with age (10). Elderly patients may be more susceptible to cardiotoxicity due to their age-related decrease in myocardial volume from cardiomyocyte loss and an increase in interstitial fibrosis. A study using cardiovascular magnetic resonance imaging (CMR) demonstrated that left ventricular mass has an inverse relationship with anthracycline dose and is a predictor of major adverse cardiovascular events (26). Therefore, elderly patients with a lower baseline myocardial volume may especially be vulnerable for cardiotoxicity, further loss of myocardial volume, and consequently, increased adverse cardiovascular outcomes. No specific recommendations regarding dose reductions can be made due to sparse data on cardiac dysfunction and left ventricular volume. A cumulative dose greater than 450 mg/m² is generally limited due to the risk of cardiac dysfunction, and most oncologists typically attempt to limit doses above 300 mg/m² if possible in patients of all age groups (27). Although no guidelines are currently set for an upper limit of anthracycline dose in older patients, it may be prudent to have lower limits in elderly patients identified at risk for cardiotoxicity (27). Several randomized control trials have evaluated different formulations of anthracyclines in order to minimize cardiotoxicity (28–30). Continuous infusions of epirubicin and doxorubicin are associated with lower cardiotoxicity when compared with a bolus infusion (30). Similarly, studies have demonstrated lower cardiotoxicity with epirubicin when compared with doxorubicin. Liposomal doxorubicin has been shown to have decreased cardiotoxicity while maintaining efficacy in randomized control trials (28–30). A single-arm phase II multicenter trial evaluated liposomal doxorubicin for treatment of large B-cell lymphoma in 80 patients aged 60 years or older (28). Cardiac events defined as Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher, were observed in only 4%, with an asymptomatic decline in left ventricular systolic function noted in 20% (28). While this study did not compare liposomal doxorubicin to standard doxorubicin, previous studies have documented significantly higher cardiac toxicity in older patients receiving standard doxorubicin-containing regimens. In the CAPRICE study of elderly or cardiotoxicity-prone patients with high-risk breast cancer, a regimen including liposomal doxorubicin,

cyclophosphamide, and paclitaxel resulted in no significant decrease in left ventricular systolic function while achieving a pathological complete response rates comparable to regimens with standard doxorubicin (29).

Although not specifically in elderly patients, dexrazoxane infusion before anthracycline therapy has been demonstrated to mitigate cardiotoxicity (31, 32). A multicenter, phase III trial of a 164 patients with breast cancer showed a 39% versus 13% fewer cardiac events and 11% versus 1% incidence of heart failure in those treated with dexrazoxane versus no dexrazoxane; treatment efficacy was similar (33). Further studies are needed on the use of dexrazoxane for the prevention of cancer treatment-related cardiotoxicity in the elderly.

Trastuzumab

Trastuzumab is frequently used in the therapy for breast cancer and in a growing number of other cancers which overexpress human epidermal growth factor 2 or HER2 neu. In these tumors, treatment with trastuzumab greatly improves outcomes; trastuzumab, however, also has the potential to cause cardiotoxicity manifested as left ventricular systolic dysfunction. The incidence of cardiotoxicity has been estimated anywhere between 2% to as high as 26% (34–36) and has been noted to be independent of the cumulative dose. The broad range in incidence speaks to the varied regimens used including monotherapy, in combination with taxanes, and in combination with anthracyclines, where it has the highest incidence (35). In a large population study of 9,535 patients with a median age of 71 years, those treated with trastuzumab had an overall increased incidence of cardiotoxicity when compared with those not treated with trastuzumab - 29.4% versus 18.6% (35). Furthermore, a competing risk regression model utilizing patients aged 66–70 years as the reference category, noted an incremental increase in risk of cardiac dysfunction with age, noting the highest risk in those 76 years of age or older and those with pre-existing comorbidities (35). Despite the concern for cardiac toxicity, trastuzumab continues to be frequently used due to its high efficacy in treatment of HER2-positive breast cancer (37–39). Advancing age is a risk factor for developing cardiac dysfunction; however, shortening therapy is not recommended in this group due to the therapeutic benefit in breast cancer. Screening recommendations are discussed later in this article. In those with evidence of cardiac dysfunction following therapy, following thorough review of benefits and risk of treatment, decision to discontinue or hold treatment should be made by the primary oncologist in close collaboration with a cardiologist.

Fluoropyrimidines

Fluoropyrimidines are associated with the risk cardiotoxicity estimated between 4–7% and consisting of angina, hypertension, arrhythmia (19). The most common toxicity is anginal chest pain, but myocardial infarction, arrhythmias and heart failure have also been reported (19). One small study estimated a 5.5 times higher risk in patients with pre-existing cardiac comorbidities (40). A dose-dependent toxicity is observed, and patients with pre-existing cardiac risk factors are at increased risk (19, 40). Fluoropyrimidine-related cardiotoxicity can also recur with rechallenge. Older patients are at risk for this toxicity due to the increased prevalence of cardiovascular risk factors in this age group.

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKI) are small molecule inhibitors that are used in targeted therapy directed at specific cell signaling pathways in several cancers (41). Lapatinib, a TKI inhibits HER2 kinase which is in the same pathway as trastuzumab, but has a decreased risk of cardiotoxicity when compared with trastuzumab (34). In a meta-analysis of 44 clinical studies, 1.6% of 3,689 patients treated with lapatinib were noted to have cardiotoxicity defined as asymptomatic decline in left ventricular systolic function, which was ultimately reversible (19, 34, 42, 43). Other TKIs such as sunitinib and sorafenib have reported cardiotoxicities as high as 11% including an asymptomatic decrease in left ventricular systolic function and a small proportion with heart failure (44–46). It is unclear whether potential cardiotoxicities are shared by the class of drugs or are specific to the molecule inhibited. Current evidence, including the studies above, have seldom outlined toxicities by age, and have primarily assessed younger patient groups. More clinical studies are needed to assess cardiotoxicity in older patients receiving these novel agents (10, 19).

Radiation Therapy

Radiation therapy, which is often used in Hodgkin lymphoma and breast cancer, may be followed by cardiotoxicity including radiation-induced coronary artery disease, valvular disorders, constrictive pericarditis, and cardiomyopathy (47). In a population-based, case-control study of 2,138 patients with breast cancer treated with left-sided or right-sided radiation therapy there was an increase in ischemic heart disease and major coronary events with a linear increase of major coronary events with the dose of radiation, within the first five years and at least 20 years after radiation therapy (48). Of note, the proportional increase in major coronary events was similar in women with and without cardiac risk factors at the time of therapy, but was overall higher in patients with pre-existing cardiac disease. Not surprisingly, there was also an increase in major coronary events in older patients especially those with pre-existing cardiac risk (48). In a large registry-based study using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program of 27,283 women, patients that received radiation therapy between the years 1973–1979 for left-sided compared with right-sided breast cancer had a statistically significant increase in ischemic heart disease (49). In subsequent years, 15-year mortality from ischemic heart disease decreased from 13% in patients treated in the mid-1970s to 5.8% in the late 1980s and there was no statistically significant difference between left- and right-sided breast cancers (49). The authors concluded these results were secondary to improved shielding and decreased radiation doses over the years (49). While this is encouraging, there are few data specific to the elderly patients on the risk-stratification for, and administration of radiation therapy.

Prevention

Multi-disciplinary Approach to Care of the Older Patients with Cancer

An individualized assessment of patient risk factors is critical in preventing cancer treatment-related complications. Often overlooked, chronologic age is not a reliable indicator of potential comorbidities or frailty (50). Undertreatment and poorer cancer-related

outcomes are dangers of using absolute age as a definitive guide for treatment. Use of a comprehensive geriatric assessment (CGA) in the care of elderly patients has the potential to improve outcomes and aid in risk stratification. In recent years, many have advocated for a multi-disciplinary approach including oncologists, cardiologists, pharmacists, and geriatricians (20). Studies evaluating CGAs typically focus on factors such as functional status, cognitive abilities, emotional conditions, comorbid conditions, nutritional status, polypharmacy and environmental situation (51). Standard oncologic evaluations such as the Eastern Cooperative Oncology Group (ECOG) scale and the Karnofsky Performance Scale (KPS) have been noted to poorly predict treatment-related complications in elderly patients (52). In a study by Ghosn et al., an abridged geriatric assessment, incorporating the factors listed above, performed better than the Karnofsky Performance Scale (KPS) and the Physical Performance Test (PPT) in predicting mortality in elderly patients with cancer (52). In a recent consensus statement, the International Society of Geriatric Oncology has recommended incorporating the factors listed above into routine geriatric assessments, but did not find sufficient evidence to recommend any one particular CGA (53). Similarly, the National Comprehensive Cancer Center guidelines have a separate section on the older patient outlining the importance of risk factor assessments in the aging population, particularly related to cardiac toxicity (54). There is a need for evidence on the role of geriatric assessments for risk stratification and on effective ways to incorporate them into routine oncologic practice (55).

Identification of The Higher Risk Older Patient

Risk stratification remains difficult in elderly patients at risk for cardiotoxicity. A comprehensive evaluation of cardiovascular comorbidities such as hypertension, diabetes, dyslipidemia, and smoking need to be evaluated prior to start of therapy (27). Those patients receiving high-dose anthracyclines, high-dose radiation, and history of prior cardiac disease are at greatest risk for cardiac dysfunction are at highest risk for cardiotoxicity (10). Cancer-specific mortality is often higher in older patients, likely due to the impact of age-related factors (35, 56). Evidence from observational studies suggests possible undertreatment, as elderly patients are frequently offered lower doses of chemotherapy due to concern for cardiotoxicity (8, 57). Additionally, alternative treatments exist in some instances, data continue to show significantly better cancer-specific outcomes with first-line treatments such as anthracyclines and trastuzumab in some patient populations (9, 58–61). This finding highlights the balance that is needed between minimizing cardiotoxic therapies and improving cancer-specific outcomes by identifying high risk elderly patients.

Pre-treatment evaluation of left ventricular systolic function is a standard part of many treatment protocols and current SIOG recommendations. However, the utility of this approach has been debated due to a low prevalence of asymptomatic left ventricular systolic dysfunction, with this strategy missing most patients that will ultimately have cardiotoxicity (62). Serum biomarkers may be useful in predicting cardiotoxicity and the role of baseline assessment of serum biomarkers prior to cancer treatment in predicting cardiotoxicity is being evaluated (63). Imaging biomarkers are also promising, and the role of pre-existing fibrosis on CMR to predict cardiotoxicity is currently being investigated (64).

A study utilizing the SEER database validated a risk score to help identify those at risk for heart failure or cardiomyopathy in patients of all ages receiving trastuzumab (65). Patients were stratified into low, intermediate, and high risk; while incorporating readily accessible risk factors such as age, chemotherapy type, coronary artery disease, atrial fibrillation/flutter, diabetes mellitus, hypertension, and renal failure (65). Similar risk score assessments should be studied to aid in a more objective assessment of risk in older patients receiving other cardiotoxic therapies.

Medications

Small randomized controlled trials have evaluated the utility of using mainstays of heart failure therapy, renin angiotensin inhibitors, aldosterone inhibitors and beta-blockers, as preventive therapy for chemotherapy-related cardiotoxicity (31, 66–71). None of these studies looked solely at older patients, but neither were they excluded. The OVERCOME trial looked at a small randomized control group of 90 patients (mean age 50 years) diagnosed with hematologic cancers and demonstrated prevention of left ventricular systolic dysfunction in those treated with prophylactic enalapril and carvedilol, compared with placebo (70). The PRADA trial, a randomized controlled trial comparing candesartan and metoprolol in patients treated for early breast cancer with anthracyclines and trastuzumab, indicated a protective effect of candesartan against left ventricular systolic dysfunction without a similar benefit for metoprolol (72). In the MANTICORE 101-Breast trial, perindopril and bisoprolol each attenuated trastuzumab-related declines in left ventricular systolic function, but did not prevent concurrent left ventricular remodeling, which was the primary outcome measure (73). In a double-blind, placebo-controlled study of spironolactone given simultaneously with anthracycline therapy, spironolactone had a protective effect in the development of left ventricular systolic dysfunction (71). Despite the favorable evidence presented above, routine prophylactic use of these therapies for cardiotoxicity is limited by the lack of consensus, as noted in two meta-analyses with differing conclusions on the benefits of these preventive strategies (32, 74). This is likely because of the heterogeneous nature of the studies included in the meta-analyses and the small numbers in each individual trial. There are several ongoing clinical trials with no upper limit for age evaluating the utility of beta blockers, ACE inhibitors, and statins in prevention of chemotherapy induced cardiotoxicity (75–79).

Although, prophylactic use of these medications has limited evidence currently, treatment of risk factors such as diabetes, hypertension, hyperlipidemia and smoking are important considerations (10). Aggressive treatment of hypertension utilizing beta-blockers, ACE-inhibitors, and ARBs should be considered in patients receiving cardiotoxic therapies.

Exercise

Aerobic exercise has evidence suggesting its use for anthracycline-induced cardiac injury as a preventive and treatment strategy (80). The evidence supporting exercise is well established in pre-clinical animal studies, noting aerobic exercise as an effective prophylactic method in prevention of left ventricular systolic dysfunction (80). Studies in humans have documented improvements of psycho-social parameters in patients receiving

cancer treatment (81). Studies investigating the effects of exercise training during breast cancer treatment on prevention of cardiotoxicity are limited. The only study on this topic, by Haykowsky, et al., showed that aerobic training did not prevent trastuzumab-related left ventricular remodeling or decline in left ventricular ejection fraction after four months of treatment in women with HER2-positive breast cancer (82).

Surveillance

Imaging

Current recommendations for imaging surveillance include monitoring of left ventricular systolic function during treatment with both anthracyclines and trastuzumab. Current National Comprehensive Cancer Network guidelines suggest cardiac monitoring at baseline, three, six, and nine months after initiating therapy for trastuzumab therapy, upon completion of treatment, and every six months for two years following completion of treatment (83). Additionally, the current International Society of Geriatric Oncology (SIOG) guidelines recommended regular monitoring of left ventricular systolic function with echocardiography or multiple gated acquisition scanning (MUGA) every two to three cycles of anthracyclines in patients 70 years of age or older (19, 27). Further attention is needed in those who have an LVEF drop of 10% even if it remains within the normal range (27). Early identification of left ventricular dysfunction is vital to stop worsening and to identify patients that may benefit from cardioprotective treatments. In a prospective study of 2625 patients with no upper age limit and median age of 51, observed a dose-dependent cardiotoxicity in patients receiving anthracyclines most often within the first year of treatment, along with the observation that close monitoring allowed for early detection and treatment of cardiotoxicity (23). The authors hypothesized, early identification of left ventricular dysfunction, in a potentially reversible phase of injury, allowed for early start of heart failure therapies and recovery of baseline LVEF (23).

Novel echocardiographic techniques are gaining traction as possible early predictors of cardiotoxicity. In cross-sectional studies, tissue Doppler imaging showed promise as an early predictor of adverse cardiac outcomes prior to onset of left ventricular dysfunction (72, 84). Myocardial deformation (strain) has garnered increasing interest as an early predictor of left ventricular systolic dysfunction. In an expert consensus statement, Plana et al., advocate for global longitudinal strain (GLS) as the optimal parameter for early detection of sub-clinical left ventricular dysfunction (85). Cardiac fibrosis identified using CMR also holds promise for the early detection of cardiotoxicity and warrants further study (86). These novel imaging techniques are gaining traction and data are warranted to help in the early or subclinical identification of cardiotoxicity in older patients. Currently, routine screening for left ventricular systolic function remains the standard of care with echocardiography and CMR as the imaging modalities of choice. MUGA is less preferable as the imaging modality of choice for surveillance due to its use of ionizing radiation in a patient population that requires serial studies. With 12 months of adjuvant trastuzumab as the standard of care, this translates into a minimum of nine studies, associated with a significant dose of ionizing radiation and the risk of radiation-related secondary cancers. A recent publication highlighted this issue through the case of a patient with multiple myeloma who received 17

MUGAs, corresponding to an effective radiation dose of 113 mSv, over a span of three years (87).

Serum Biomarkers

High sensitivity troponin has been evaluated as a possible early predictor for cardiotoxicity during cancer treatment (88–91). A study of 703 patients treated with high-dose anthracyclines, evaluated the prognostic value of serial high-sensitivity cardiac troponin at preset time points on start, 12, 24, 36, and 72 hours, and one month after each dose of high-dose anthracycline therapy (91). The incidence of cardiovascular events, defined as heart failure, asymptomatic decline of left ventricular systolic function, and arrhythmias, was noted at 87% in the group with both early and late troponin elevation, 37% with only early elevated troponin and 1% with negative troponin values (91). A similar study in patients receiving trastuzumab with troponin elevation identified those at risk for major adverse cardiac events and irreversible cardiotoxicity (90, 92). The use of NT-proBNP has been limited to clinically appropriate settings such as patients presenting with signs and symptoms of heart failure (93). The evidence on the use of biomarkers in predicting patients at risk for cardiotoxicity is limited and more studies are needed before recommendations are made regarding routine use of biomarkers for surveillance including in older adults.

Treatment of Cardiotoxicity

Heart failure and cardiomyopathy from cancer treatments should be treated according to the standard ACC/AHA guidelines for the evaluation and management of heart failure (94). This generally includes the traditional mainstays of heart failure treatment: beta blockers, ACE-inhibitors, angiotensin II receptor blockers, aldosterone antagonists, and diuretics. Exercise training and cardiac rehabilitation likely have similar efficacy in this group as well.

Summary

In conclusion, significant evidence suggests that older patients are more susceptible to cancer-treatment related cardiotoxicity compared to their younger counterparts. Barriers such as pre-existing comorbidities, the potential for undertreatment and under-representation in clinical trials remain. There is a need for close collaboration between clinicians in a multi-disciplinary approach. Clinical studies are urgently needed on the prevention, early detection, and treatment of cardiotoxicity in older cancer survivors.

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Figure 1. The “snowball effect” resulting in cardiovascular complications of cancer therapy in older adults. See text for details. Adapted with permission from Shenoy et al. (13)