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REVIEW ARTICLE

Cardiac Effects of Anticancer Therapy in the Elderly

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ABSTRACT

Cancer incidence increases with age, and as life expectancy increases, the number of elderly patients with cancer is increasing. Cancer treatments, including chemotherapy and radiotherapy, have significant short- and long-term effects on cardiovascular function. These cardiotoxic effects can be acute, such as changes in electrocardiogram (ECG), arrhythmias, ischemia, and pericarditis and/or myocarditis-like syndromes, or they can be chronic, such as ventricular dysfunction. Anticancer therapies can also have indirect effects, such as alterations in blood pressure, or can cause metabolic abnormalities that subsequently increase risk for cardiac events. In this review, we explore both observational and clinical trial evidence of cardiac risk in the elderly. In both observational and clinical trial data, risk of cardiotoxicity with anthracycline-based chemotherapy increases with age. However, it is less clear whether the association between age and cardiotoxicity exists for newer treatments. The association may not be well demonstrated as a result of under-representation of elderly patients in clinical trials and avoidance of these therapies in this population. In addition, we discuss strategies for surveillance and prevention of cardiotoxicity in the elderly. In the elderly, it is important to be aware of the potential for cardiotoxicity during long-term follow-up and to consider both prevention and surveillance of these late effects.

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INTRODUCTION

Cancer incidence increases with age, and as life expectancy increases, there are rising numbers of elderly patients with cancer. In the next 10 years, 70% of newly diagnosed patients with cancer will be older than age 65 years.[1] The elderly are historically under-represented in clinical trials, with patients older than age 65 years representing only 38% of enrolled patients.[2] For this reason, less is known about long-term risks in this population of cancer survivors.

Cancer treatments, including chemotherapy, targeted therapy, radiotherapy (RT), and hormonal therapy, have multiple short- and long-term toxicities, but one of the most concerning is cardiac toxicity. Cardiotoxicity includes acute events, such as arrhythmias, acute coronary syndrome, and pericarditis- and/or myocarditis-like syndromes, as well as chronic conditions, such as systolic and diastolic left ventricular dysfunction.[3] Drugs can affect the cardiovascular system either through direct effects to cardiac myocytes resulting in cardiomyopathy, or indirect effects, such as hypertension, which subsequently increase the risk of cardiac disease.[4] Known cardiotoxicities and proposed mechanisms of antineoplastic agents are summarized in Table 1.

ANTHRACYCLINE-INDUCED CARDIOTOXICITY

Anthracyclines are classically associated with congestive heart failure (CHF); however, they can also cause acute cardiotoxicity, such as electrocardiogram (ECG) changes, arrhythmias, and pericarditis and/or myocarditis syndromes, but this is rare.[5,6] Acute anthracycline-induced toxicities are generally reversible and do not predispose patients to later onset CHF.[7] The mechanism for cardiotoxicity is thought to include formation of free radicals, induction of apoptosis, decrease in cardiac contractility via changes in intracellular adenosine triphosphate production, drug-related depression of cardiac glutathione peroxidase activity, and mitochondrial DNA damage leading to respiratory defects and/or interference with topoisomerase II (Table 1).[5] One large single-institution study found that median survival of those with anthracycline-induced cardiomyopathy was approximately 1 year.[8] In that study, age was found to be an independent risk factor with a 20% increase in risk for each decade of life.[8]

Clinical Trials Data

A retrospective combined analysis of three doxorubicin-based clinical trials conducted between 1988 and 1992 reported that incidence of doxorubicin-induced CHF was associated with cumulative dose and age. Risk was 2% at a cumulative

Table 1. Cardiovascular Toxicity of Anticancer Therapy[4a,5,7,9,10,34,43,44,60]

Agent	Toxicity	Proposed Mechanisms	Age-Related Toxicity
Anthracyclines	Left ventricular dysfunction CHF Pericarditis and/or myocarditis	Generation of reactive free radicals Induction of apoptosis Changes in ATP production Mitochondrial DNA damage Downregulation of mRNA expression for sarcoplasmic reticulum calcium ATPase	Increased risk at age > 65 years Risk increases as cumulative dose increases
Fluorouracil and/or capecitabine	Angina Myocardial infarction Arrhythmia CHF Cardiogenic shock Sudden death	Vasospasm Direct myocardial toxicity Coronary artery thrombosis Development of arteritis Induction of apoptosis	Unknown
Bortezomib	Left ventricular dysfunction CHF	Induction of endoplasmic reticulum stress after proteasome inhibition	Unknown
Cyclophosphamide	CHF	Direct endothelial injury Intracapillary microemboli Coronary vasospasm	Unknown
Docetaxel and/or paclitaxel	CHF Myocardial ischemia Bradycardia	Cremophor EL vehicle induction of histamine release Effects on Purkinje system and/or extracardiac autonomic control	Unknown
Cisplatin	Thrombosis	Platelet activation and aggregation Disruption of endothelial integrity Elevated von Willebrand factor leading to vasospasm	Unknown
Trastuzumab	Left ventricular dysfunction CHF	Inhibition of HER2 ATP depletion Disruption of mitochondrial integrity	Increased risk at age > 80 years
Bevacizumab	CHF Arterial thrombosis Angina Myocardial infarction Hypertension	Inhibition of VEGF Reduction in nitric oxide and prostacyclin Reduction of myocardial capillary density Cardiac fibrosis	Inconclusive
Lapatinib	Left ventricular dysfunction CHF QT prolongation	Inhibition of HER2 ATP depletion Disruption of mitochondrial integrity	Unknown
Imatinib	CHF	Inhibition of c-Abl	Unknown
Dasatinib	CHF QT prolongation	Inhibition of c-Abl Inhibition of Src	Unknown
Nilotinib	QT prolongation	Unknown	Unknown
Sunitinib	CHF Hypertension	Mitochondrial damage Inhibition of tyrosine kinase that regulates hypertensive stress in myocardiocytes Induction of apoptosis ATP depletion Inhibition of VEGF	Unknown
Sorafenib	Myocardial ischemia Hypertension	Inhibition of VEGF Induction of apoptosis	Unknown
Erlotinib	Myocardial ischemia Myocardial infarction Thrombosis	Unknown	Unknown
Thalidomide and/or lenalidomide	Thrombosis Bradycardia	Interaction of platelets and endothelium Increased platelet aggregation and von Willebrand factor Activation of vasovagal pathway	Unknown
Arsenic trioxide	QT prolongation	Prolongation of action potential	Unknown
Histone deacetylase inhibitors	Thromboembolism QT prolongation	Unknown	Unknown
Radiotherapy	Coronary artery disease Acute pericarditis Myocarditis CHF Valvular disease Conduction disease	Generation of reactive oxygen species Endothelial damage Development of arteritis Development of cardiac fibrosis	Unknown

Abbreviations: ATP, adenosine triphosphate; CHF, congestive heart failure; HER2, human epidermal growth factor receptor 2; mRNA, messenger RNA; VEGF, vascular endothelial growth factor.

dose of 200 mg/m^2, 5% at 400 mg/m^2, 16% at 500 mg/m^2, and 26% at 550 mg/m^2. Patients older than age 65 years had a two-fold risk of developing doxorubicin-induced CHF compared with younger patients after adjusting for history of cardiovascular disease, low-normal baseline ejection fraction (EF), performance status, and sex. However, at doses of 400 mg/m^2, the likelihood of developing CHF increased three-fold.[7,9]

In a meta-analysis of eight doxorubicin-based trials, the incidence of CHF was 2.2% among patients treated from 1970 to 1977.[10] Risk factors included the cumulative dose and age. No absolute cutoff point was defined for total dose; however, the slope of the curve steepened at a cumulative dose of 550 mg/m^2. That study demonstrated that CHF risk was age-related, but as dose increased, the risk of CHF with advancing age became more dramatic.

Anthracycline administration techniques may also affect cardiac risk in the elderly. Robert and Hoerni,[11] assessed clearance of doxorubicin and reported a significant correlation between clearance of doxorubicin and age, with older patients having lower clearance. A Cochrane review of seven randomized trials that addressed the duration of anthracycline infusions reported decreased CHF following infusions of more than 6 hours compared with shorter infusions (relative risk, 0.27), and longer infusions were not associated with a reduced response rate or survival. In addition, liposomal formulations have been associated with lower risk of cardiotoxicity. A meta-analysis demonstrated a lower risk of heart failure in patients who received liposomal-encapsulated doxorubicin compared with conventional doxorubicin (relative risk, 0.38; 95% CI, 0.24 to 0.59).[12] Thus, longer infusions and consideration of liposomal formulations may be a better approach for high-risk elderly patients.

Observational Data That Define Risk

Retrospective studies suggest that cardiovascular disease risk factors, such as history of hypertension, diabetes, or known coronary artery disease (CAD), also increase the risk of developing cardiotoxicity from anthracyclines.[13,14]

The Surveillence, Epidemiology, and End Results (SEER)-Medicare database links data from the SEER registry, which collects demographic, tumor, cancer treatment, and survival data on approximately 25% of the US population, with billing claims from Medicare. This database provides information about initial diagnosis and subsequent medical care, including details about treatment, complications, and survival. Because the majority of patients age 65 or older receive Medicare, this is an important tool in evaluating outcomes in this elderly population.[15] A large retrospective cohort study used the Medicare database to evaluate the cardiac effects of chemotherapy in 31,748 patients with early-stage breast cancer. Elderly patients treated with doxorubicin were 2.5 times more likely to develop cardiomyopathy than patients who did not receive chemotherapy.[16] A similar study evaluated 43,338 women 66 to 80 years old with breast cancer and found that after 10 years, 38% of women treated with anthracyclines developed CHF compared with 33% in the non-anthracycline group and 29% in the no-chemotherapy group. Other predictors of CHF included age, black race, stage, trastuzumab treatment, hypertension, diabetes, CAD, peripheral vascular disease, and chronic obstructive pulmonary disease.[17]

A related SEER-Medicare study evaluated 6,388 patients with diffuse large B-cell lymphoma who were treated with anthracycline-based chemotherapy and specifically focused on cardiac risk factors. Cardiac risk factors were common; 31.9% had claims for diabetes, 73.1% for hypertension, and 53.6% for hyperlipidemia. Pre-existing heart disease was also common; 2.1% had claims for previous myocardial infarction, 22.2% for pre-existing CHF, and 50.9% for pre-existing heart disease. In the population evaluated, 42.4% received doxorubicin-based chemotherapy. Subsequent CHF was increased in patients who received doxorubicin, with a hazard ratio (HR) of 1.29. Risk of CHF also increased proportionally with the number of doxorubicin treatments and increasing age. Risk was associated with the number of comorbidities, presence of cardiac risk factors (hypertension, diabetes, previous CAD), or other pre-existing heart disease.[18]

FLUOROPYRIMIDINES

Fluoropyrimidines, such as fluorouracil (FU), have been associated with acute myocardial ischemia. The most common symptom is angina-like chest pain, but myocardial infarction has been reported along with arrhythmia, heart failure, cardiogenic shock, and sudden death.[5,6] Although the pathogenesis of cardiotoxicity is unknown, proposed mechanisms include effects on the vasculature, such as coronary artery thrombosis, arteritis, or coronary vasospasm and direct myocardial toxicity, such as accumulation of metabolites that interfere with cellular metabolism and apoptosis leading to inflammatory lesions which could mimic myocarditis.[5] Risk factors include a history of CAD, previous mediastinal RT, and concomitant cisplatin therapy.[19] Toxicity appears to be dose dependent and infusion-rate dependent.[5,19] Capecitabine can also cause symptoms of angina, with the main risk factor for development of angina being pre-existing CAD.[5] Because risk of developing coronary vascular disease increases with age, it is important to be mindful of the potential toxicities and risk factors in elderly patients.[20] Individual case reports have suggested that calcium channel blockers may prevent fluoropyrimidine-induced cardiac ischemia.[21,22] The issue of rechallenging patients who have developed fluoropyrimidine cardiotoxicity remains controversial. The current consensus is to rechallenge only those patients who do not have alternate therapy options available and to do so in a monitored setting.[5,23,24]

Clinical Trials Data

A large prospective study by de Forni et al,[25] evaluated the cardiotoxicity of FU. In that study, 7.6% of patients experienced a cardiac event, and 32% of those patients had underlying cardiac disease. Mean onset of time to cardiac symptoms was 3 days, and events included angina (64%), hypertension (18%), and arrhythmia (4%), along with hypotension, malaise, and dyspnea. ECG repolarization abnormalities were observed in 65% of the patients with cardiac events. A prospective study found evidence of silent ischemia diagnosed by ECG changes in 67% of patients undergoing continuous infusion who were monitored for 24 hours.[26] In a phase II trial of different dosing schedules of capecitabine, with an average age between 62 and 65 years, 4% experienced chest pain, angina, or atrial fibrillation.[27] A phase III study compared oral capecitabine with intravenous FU in patients with metastatic colorectal cancer and reported no difference between the groups. The average age in that study was 64 years.[28] Finally, in a randomized phase II trial of different irinotecan schedules in combination with capecitabine, there were two deaths (1.4%) secondary to myocardial infarctions, and both patients had cardiac risk factors.[29]

Table 2. New York Heart Association Functional Classification

Class	Functional Classification
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. Comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or angina pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

BIOLOGIC THERAPIES

Trastuzumab

Trastuzumab-induced cardiotoxicity is likely related to inhibition of cardiomyocyte human epidermal growth factor receptor 2 (HER2, also known as ErbB2), which leads to interference with normal growth, repair, and survival of cardiomyocytes. Trastuzumab binding to HER2 may also lead to contractile dysfunction via disruption of mitochondrial integrity.[5] The risk of cardiotoxicity increases when anthracyclines are administered concurrently or sequentially with trastuzumab.[30]

Clinical trials data. The cardiotoxicity of trastuzumab was first observed in a phase III trial in women with metastatic breast cancer.[31] Of those who received trastuzumab, 28% developed cardiac dysfunction as classified by New York Heart Association criteria (Table 2),[31a] the majority in women who received both an anthracycline and trastuzumab. The mean age for women in that trial was 53 years old. Cardiotoxicity decreased significantly in trials when anthracyclines and trastuzumab were given sequentially rather than in combination. A multicenter randomized trial of 3,387 women with a median age of 49 (only 16.2% were age 60 years or older) evaluated trastuzumab use after completion of neoadjuvant or adjuvant chemotherapy and found a 9% incidence of cardiotoxicity (decrease in left ventricular ejection fraction [LVEF], CHF, and/or death as a result of cardiac causes).[32] Finally, an adjuvant breast cancer trial randomly assigned 3,222 women who were required to have an EF of more than 50% to enroll and were monitored every 12 weeks for change in EF. In that study, 47% of women were older than age 50 years. The incidence of cardiotoxicity was highest (20.6%) in the group that received anthracycline followed by a taxane and trastuzumab, 11.9% in the group without trastuzumab, and 9.8% in the group that received trastuzumab concurrently with non-anthracycline–based chemotherapy.[33]

Observational data that define risk. A retrospective population-based cohort study using data from the Cancer Research Network evaluated 12,500 women with early-stage breast cancer to determine the rates of anthracycline and trastuzumab use along with their association with development of heart failure and/or cardiomyopathy. The mean age of women in this population was 60 years. At 5 years of follow-up, the incidence of heart failure and/or cardiomyopathy was 4.3% for women who received anthracyclines alone, which was similar to the incidence of heart failure and/or cardiomyopathy in women who received other chemotherapy. In women who received trastuzumab without anthracycline chemotherapy, the cumulative incidence was 12.1%, and in the group that received anthracycline plus trastuzumab, it was 20.1%.[33a] A recent population-based study that used the SEER-Medicare and the Texas Cancer Registry-Medicare databases in women age $\geq$ 66 years with early-stage breast cancer treated with chemotherapy evaluated the rates and risk factors associated with CHF. A total of 9,535 patients were evaluated, with a median age of 71 years; of this group, 23.1% received trastuzumab. The incidence of CHF was 29.4% in those who received trastuzumab and 18.9% in those who did not receive trastuzumab. Among patients who received trastuzumab, risk factors for CHF included age older than 80 years (HR, 1.53), cardiac comorbidities such as CAD (HR, 1.82) and hypertension (HR, 1.24), and administration of trastuzumab once per week versus once every 3 weeks (HR, 1.33). Among patients who received trastuzumab and subsequently developed CHF, 68.8% developed CHF within the first 12 months after initiation of treatment.[34]

Bevacizumab

It is hypothesized that inhibition of vascular endothelial growth factor (VEGF) by bevacizumab may lead to endothelial cell dysfunction and defects within the vascular lining, resulting in activation of tissue factor thus leading to increased risk of thromboembolism. In addition, inhibition of VEGF may cause reduction in nitric oxide and prostacyclin, which promotes vasoconstriction and increased peripheral vascular resistance potentially leading to hypertension.[5]

Clinical trials data. The incidence of hypertension in clinical trials ranged from 7% to 36%.[35-38] This variability results from the strict selection criteria for enrollment onto the trial and the definition used for the reporting of hypertension. A phase III trial of bevacizumab added to FU, leucovorin, and oxaliplatin showed an increase in grade 3 hypertension in the bevacizumab arm (12.0% *v* 1.8%). In that study, 41.8% of participants were age 60 years or older.[39] A phase II trial in patients with breast cancer of dose-dense doxorubicin and cyclophosphamide plus bevacizumab initiated either concurrently or sequentially with paclitaxel was performed to evaluate safety. Toxicity was defined as a decrease in LVEF of more than 15% or more than 10% below the lower limit of normal. No difference between the arms was reported, with a cardiac toxicity rate of 15% with concurrent treatment versus 12% in the sequential treatment arm. In that study, 12% of patients experienced grade 3 hypertension. The median age of women in that study was 50 years.[40] A recently reported trial of 3,509 women with HER2-positive breast cancer were randomly assigned to a trastuzumab-containing regimen with or without bevacizumab. The bevacizumab group had significantly higher rates of hypertension (10% *v* 4%; $P < .001$) and CHF (2.1% *v* < 1%; $P = .021$).[41]

Observational data that define risk. A study using the SEER-Medicare database investigated the use of bevacizumab for patients with metastatic colorectal cancer. Patients age $\geq$ 80 years or with pre-existing cardiac conditions, CHF, or arrhythmias were less likely to receive bevacizumab.[42] In addition, an analysis of patients older than age 65 years with multiple cancers reported that 35.5% of elderly patients who had received bevacizumab had a contraindication before its receipt, including 19% with cardiac disease. In the group

that received bevacizumab without bevacizumab contraindications, 10.6% developed subsequent cardiac disease compared with 1.5% reported in the clinical trials.[43,44]

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKIs) are small-molecule targeted therapeutics that are directed against specific molecules and signaling pathways.[45] Although many drugs in this class are similar, they differ in their specific targets or combination of targets and thus result in a variety of toxicities. Mechanisms of cardiotoxicity differ on each drug's target; for example, the proposed mechanism for sunitinib use that results in CHF may be related to mitochondrial damage in cardiomyocytes or activation of apoptosis and interference in cellular metabolism.[5] CHF related to use of lapatinib may be a result of HER2 inhibition.[5] Hypertension related to use of sunitinib and sorafenib may be related to inhibition of VEGF.[5] Given differences in both mechanism of action and subsequent toxicities in TKIs, it is currently unclear whether cardiotoxicity is a drug-specific or class-specific phenomena; there is insufficient evidence to guide clinicians in the safety of switching drugs within this class after a toxicity occurs.

Clinical trials data. Sunitinib received US Food and Drug Administration approval for the treatment of GI stromal tumor and renal cell carcinoma in 2007 after two phase III trials demonstrated efficacy.[46-48] In the study evaluating sunitinib for treatment of GI stromal tumor, 11% of patients in the sunitinib arm had treatment-emergent LVEF. Of those, 41% recovered without intervention, 14% had persistent CHF, and 9% died.[46,49] The median age in the sunitinib group was 58 years; toxicity effects by age were not reported.[46] In a trial of sorafenib, cardiac ischemia or infarction was reported in 4.9% of patients assigned to sorafenib. Median age for this trial was 58 years, and adverse events were not broken down by age.[50,51]

A combined analysis of lapatinib clinical trials that included 3,689 patients reported that 2% experienced cardiac events. Of the patients with cardiac events, 23% were older than age 70 years.[52] A retrospective review of six imatinib registration trials reported that the incidence of CHF was 0.5%.[53] A phase III trial of dasatinib reported a 7% incidence of cardiotoxicity; however, the mean age of the patients was 45 years.[54] The incidence of QT prolongation with nilotinib is 1% to 10% and, as a result, nilotinib carries a black box warning for QTc prolongation.[55] In a phase II study of patients with median age 57 years, Qtc prolongation was reported in 4% of patients.[56]

Observational data that define risk. The evidence of cardiotoxicity related to TKIs was first reported in a case series of 10 patients who developed CHF while taking imatinib. All patients had a normal LVEF before initiation and presented with symptoms corresponding to New York Heart Association class III to IV heart failure (Table 2). Mean LVEF was 25%, the mean age of patients was 64 years, and 50% of those patients were older than age 65 years.[57,58]

A single-institution prospective cohort study of 74 patients with metastatic renal cell carcinoma who were intended to start TKI therapy with sorafenib or sunitinib were evaluated for CAD risk factors, evidence of CAD, hypertension, rhythm disturbances, and CHF during treatment. Monitoring included symptom assessment, ECG, echocardiography, and biochemical markers. Median age for this study population was 66 years; 33.8% of patients experienced a cardiac event (increased cardiac enzymes if normal at baseline, symptomatic arrhythmia that required treatment, new left ventricular dysfunction, or acute coronary syndrome), 40.5% had ECG changes, and 52% were symptomatic (angina, dyspnea, or dizziness).[59]

OTHER ANTINEOPLASTIC AGENTS

In addition, other chemotherapeutics have been associated with cardiotoxicity (Table 1). The relationship between cardiotoxicity risk and age is currently unknown for many of these drugs. These agents include bortezomib, cyclophosphamide, docetaxel and/or paclitaxel, cisplatin, thalidomide and/or lenalidomide, arsenic trioxide, and histone deacetylase inhibitors.[5,60]

RT

Randomized trials report that breast cancer RT can increase the risk of ischemic heart disease, presumably as a result of incidental radiation to the heart.[61-63] The mechanism of cardiotoxicity is likely secondary to generation of reactive oxygen species that disrupt DNA strands and lead to vascular endothelial damage and inflammation that leads to fibrosis.[62,64]

Clinical Trials Data

Variations in the risk of treatment-related cardiotoxicity are reported; however, they could be related to differences in technique as well as follow-up. A randomized trial of pre- or postoperative RT (45 Gy in 5 weeks) versus surgery alone in 960 women (age 71 years or younger) with early-stage breast cancer was performed with a mean follow-up of 16 years. Patients with higher doses of radiation to the myocardium were found to have a three-fold increased risk of death as a result of ischemic heart disease. The authors of this article noted that modern techniques could minimize this risk.[65] Another study randomly assigned 3,083 women aged 70 years or younger to receive RT or not following mastectomy. The risk of subsequent ischemic heart disease was similar in both groups.[66] However, Ragaz et al[67] reported a slightly increased risk of cardiac death (1.8% *v* 0.6%) after 20 years of follow-up in 318 women with breast cancer randomly assigned to receive RT or no additional treatment after mastectomy.

Observational Data That Define Risk

A large retrospective population-based study used the SEER database to identify 27,283 women with early-stage breast cancer diagnosed from 1973 to 1989 who were treated with adjuvant RT to evaluate their 15-year ischemic heart disease mortality rate. Patients were stratified into three cohorts on the basis of year of diagnosis: 1973 to 1979, 1980 to 1984, and 1985 to 1989. The mean age of patients included in that study was 57 years. The investigators found a statistically significant difference in 15-year mortality from ischemic heart disease in patients with left-sided breast cancer diagnosed from 1973 to 1979 at 13.1% compared with right-sided breast cancer at 10.2%. The cohort diagnosed from 1980 to 1984 had a 9.4% ischemic heart disease mortality rate in patients with left-sided tumors and an 8.7% rate in those with right-sided tumors; the differences were not statistically different. The cohort diagnosed from 1985 to 1989 had a 5.8% ischemic heart disease mortality rate at 15 years in those with left-sided disease and a 5.2% rate in those with right-sided disease; again there was no statistically significant difference determined by disease

locality. This study illustrates that risk of death as a result of ischemic heart disease associated with RT for breast cancer treatment has decreased over time and, similarly, the gap between left-sided mortality and right-sided mortality has also decreased over time.[68]

Darby et al[69] performed a population-based case-control study of major coronary events in women who received RT for breast cancer in Sweden and Denmark. They identified 963 women younger than age 70 years with major coronary events; 1,205 women without coronary events served as controls. The rates of major coronary events increased proportionally with mean RT dose. Left breast irradiation had higher rates of coronary events compared with right breast irradiation (HR, 1.32). A prior history of ischemic heart disease increased risk by more than six-fold. Other predictors of increased risk were risk factors for CAD, history of circulatory disease, diabetes, history of chronic obstructive pulmonary disease, smoking, obesity, and use of analgesic medications. Age at diagnosis was also associated with a statistically nonsignificant increased risk of cardiotoxicity. Few women in this study were treated with anthracyclines, and no women were treated with taxanes or trastuzumab.

However, a more recent observational study was performed to further quantify the risk of cardiotoxicity related to modern RT techniques.[70] This study derived risk estimates of cardiotoxicity from 48 women on the basis of treatment plans generated for both supine and prone treatment positions of each patient. The average cardiac RT doses were 1.37 Gy for supine-positioned RT and were less in prone-positioned RT compared with 4.6 Gy in the study by Darby et al.[69] The authors reported that the predicted lifetime risks of major coronary events as a result of RT are expected to decrease with the use of modern techniques.[70]

MONITORING AND SURVEILLANCE

Among the difficulties of evaluating data from clinical trials are the inconsistencies of definitions and terminology of adverse cardiotoxicity events. For example, consider an asymptomatic patient who develops a decrease in EF from 60% to 35% after treatment; if the event was considered "left ventricular systolic dysfunction," it would be grade 0. If the event was considered "heart failure," it would be grade 1. If the event was considered "decline in EF," it would be grade 3. A single event is, therefore, graded as 0, 1, or 3 on the basis of terminology. This leads to variance across clinical trials, which makes them difficult to compare.[48]

Current guidelines of monitoring for cardiovascular toxicity include evaluating the EF either by echocardiography or multiple gated acquisition scintography. Magnetic resonance imaging with gadolinium contrast enhancement provides detailed information regarding cardiac anatomy and EF and is able to detect subtle myocardial damage. However, this modality has not been widely studied in this context. Measurement of EF may underestimate actual cardiac damage, because patients may have subtle changes in cardiac function not detected on imaging studies.[71] Serum cardiac biomarkers, such as N-terminal prohormone brain natriuretic peptide and/or troponin, may also play a role in the detection of cardiac damage, but further investigation is needed to classify their predictive value.[72]

The International Society of Geriatric Oncology recommends regular monitoring of EF by echocardiography or multiple gated acquisition scan after every two to three cycles of anthracyclines for patients age 70 years or older.[7] They further recommend consideration of liposomal formulations, prolonged infusions, or use of dexrazoxane if there is a decrease of more than 10% in EF, even if the EF remains within the normal range. This recommendation applies especially to patients with hypertension, diabetes, or CAD.[7] There is a need for further systemic research in the risk prediction models, early biomarkers of toxicity, monitoring, and surveillance of older patients with cancer receiving treatment with cardiotoxic antineoplastic drugs because current evidence in this area is insufficient to create recommendations.

PREVENTION

Dexrazoxane, an iron-chelating agent, has been shown to reduce the risk of anthracycline-induced cardiomyopathy[73]; however, it is not routinely used in practice. The American Society of Clinical Oncology recommends its use only in patients who have received more than 300 mg/m^2 of doxorubicin-based treatment.[74] Concerns over its use include diminishing antitumor efficacy of chemotherapy, possible myelosuppression, and secondary malignancies.[75] A systematic review found no significant differences in treatment efficacy or secondary malignancies and only a small but statistically significant increase in the incidence of grade 3 to 4 anemia and leukopenia.[73]

Drugs used to treat heart failure have also shown promise in prevention of chemotherapy-induced cardiotoxicity. A study of 50 patients randomly assigned to receive prophylactic carvedilol or placebo before anthracycline chemotherapy found that beta blockers preserve EF.[75a] Similar results were seen with nebivolol.[76] A larger randomized trial that included 473 patients demonstrated that enalapril may also help prevent cardiotoxicity; however, the mean age was 45 years, and the benefits in the elderly are not known.[77] There is an ongoing randomized phase II trial evaluating lisinopril, carvedilol, or placebo for 1 year following trastuzumab.[78]

In conclusion, in both observational and clinical trial data, risk of cardiotoxicity with anthracycline-based chemotherapy increases with age. However, it is less clear whether the association between age and cardiotoxicity exists for newer treatments. The association may not be well demonstrated as a result of under-representation of elderly patients in clinical trials and avoidance of these therapies in this population. In the elderly, it is important to be aware of the potential for cardiotoxicity during long-term follow-up and to consider both prevention and surveillance of these late effects. However, despite the risks, life-saving treatments should not be avoided on the basis of age alone.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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