Cardiovascular Complications of Breast Cancer Therapy in Older Adults

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ABSTRACT

Older adults frequently have pre-existing and cancer-related risk factors for cardiovascular toxicity from cancer treatment. In this review, we discuss the risk fac-

tors and strategies for prevention and management of cardiovascular complications in older women with breast cancer. *The Oncologist* 2011;16:1138–1143

INTRODUCTION

Approximately 50%–60% of patients newly diagnosed with breast cancer are women aged >65 years [1, 2]. In the U.S., the aging of the baby boomer generation and the increase in the number of older adults will undoubtedly result in more cases of cancer in older adults [3]. Many older patients are treated with lower-intensity regimens (reduced doses of standard chemotherapy regimens or use of non-standard regimens), leading to lower response and survival rates [4, 5]. A major reason for the use of lower-intensity regimens is concern for toxicity and treatment-related mortality [6, 7]. Older patients have been found to have higher rates of toxicity [4], including cardiotoxicity [8–10], and

treatment-related mortality [4]. However, there is a paucity of prospective data on the cardiac complications of breast cancer treatment in older women because older patients are systematically underrepresented in oncology clinical trials [7, 11–13].

Cardiotoxicity from breast cancer therapy is a long-term concern. A study from the Surveillance, Epidemiology, and End Results (SEER)–Medicare database of women aged ≥65 years with long-term follow-up found that, despite selecting only patients with a favorable cardiac risk, women who were treated with chemotherapy were more likely than those who were not treated with chemotherapy to experience subsequent cardiac disease [8]. In the first year after a

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breast cancer diagnosis, the incidence of cardiotoxicity was 1.55% for patients not receiving chemotherapy and 4.09% for patients receiving anthracyclines (odds ratio, 3.51; 95% confidence interval [CI], 2.63–4.69). After 5 years of follow-up, the cumulative incidence had increased to 4.97% in patients not receiving chemotherapy and 10.23% in patients receiving a chemotherapy regimen that included an anthracycline [8].

There are multiple risk factors for cardiac complications of breast cancer therapy in older women. Baseline factors related to older age make these patients more susceptible to cardiac complications from cancer treatment. The diagnosis of breast cancer leads to changes in lifestyle and other factors that increase their vulnerability to cardiac complications. Finally, chemotherapy drugs have direct toxic effects that result in cardiac complications. The sequential impact of these factors, illustrated in Figure 1, can be conceptualized as a “snowball effect,” whereby the “snowball” formed of older age- and female gender-related factors is “set into motion” by a diagnosis of breast cancer. Changes in lifestyle and factors related to breast cancer treatment (other than the direct toxic effects of chemotherapy) add more “snow” and “momentum” to the “rolling snowball.” Finally, the addition of direct toxic effects of the chemotherapy drugs results in “breaking of the snowball,” or clinically apparent cardiovascular complications.

BASELINE RISK FACTORS

Older women are particularly vulnerable to cardiotoxicity from cancer treatment because of their baseline risk resulting from their age. Older age at the start of treatment is associated with a higher risk for anthracycline-related [8, 10, 14–19] and trastuzumab-related [20–24] cardiotoxicity. In a study of women aged >65 years from the SEER–Medicare database, age was a significant predictor of chemotherapy-related heart failure (hazard ratio, 1.79 per 10 years; 95% CI, 1.66–1.93) [10]. In a pooled analysis of three studies of anthracycline therapy, age >65 years was independently associated with a higher risk for cardiotoxicity after a cumulative doxorubicin dose of 400 mg/m² [14].

Age-related changes in drug pharmacokinetics make older patients more susceptible to the cardiotoxic effects of chemotherapy. The volume of distribution for drugs is a function of body composition, serum protein profile, and blood cells (especially erythrocytes). Decreased serum albumin levels and anemia are not uncommon in the elderly. These conditions may lead to elevated peak concentrations of chemotherapy drugs that are significantly incorporated into erythrocytes (such as anthracyclines and ifosfamide) [25] or are highly protein-bound (such as anthracyclines

and taxanes) [26, 27]. Elevated peak concentrations [28, 29] are linked to greater toxicity [30–34].

There is a decrease in the glomerular filtration rate by approximately 0.75–1 mL/minute per year over the age of 40 in over two thirds of individuals [35]. This decline in kidney function can lead to greater toxicity resulting from either reduced excretion of active drugs, such as methotrexate, cyclophosphamide, or carboplatin, or reduced excretion of active metabolites for drugs that are initially eliminated by the liver, such as anthracyclines [28, 36].

Pre-existing cardiac disease, such as coronary artery disease or cardiomyopathy, is a risk factor for anthracycline-related [8, 10] and trastuzumab-related [22, 37] cardiac complications in patients with breast cancer. Cardiac risk factors such as hypertension [15, 18, 22], diabetes [15, 18], hyperlipidemia [15], and obesity [15] have also been found to predispose to anthracycline-related cardiac complications in breast cancer patients. Cardiovascular risk factors are frequently present in cancer patients: in a hospital-based registry of >19,000 cancer patients, 38% of patients had hypertension and 11% had diabetes mellitus [38]. A study using the SEER–Medicare database, evaluating >35,000 patients, found that hospitalization for chemotherapy-induced toxicity in older patients with breast cancer increased significantly with their comorbidity score [39].

Polypharmacy, which is common in older patients with cancer, increases the risk for drug–drug interactions and chemotherapy-related toxicity [40, 41]. Clearance of chemotherapy drugs may be affected by concomitant drugs, which can lead to lower clearance of the chemotherapy, placing the patient at greater risk for toxicity. Drugs used by older patients and metabolized by the cytochrome P450 pathway, such as selective serotonin reuptake inhibitors, phenytoin, steroids, ketoconazole, and macrolide antibiotics, may interact with chemotherapy agents such as ifosfamide, vinca alkaloids, etoposide, taxanes, and aromatase inhibitors [42, 43].

CANCER-RELATED RISK FACTORS

Anemia and hypoproteinemia from malnutrition are more common in patients with cancer. Thus, the volume of distribution for water-soluble drugs is further reduced because of cancer. Older patients with breast cancer are susceptible to worsening of renal function from dehydration or hypovolemia, hyperuricemia, cachexia, and nephrotoxic chemotherapy drugs such as cisplatin and methotrexate, which in turn may increase their risk for cardiotoxicity [44, 45].

Physical inactivity and obesity—prevalent in older breast cancer patients [46]—are independent risk factors for cardiovascular disease. One study identified poor performance status and a body weight ≥ 70 kg as predictive

Figure 1. The “snowball effect” leading to cardiovascular complications of breast cancer therapy in older patients. See text for details.

factors for cardiac complications in patients with metastatic breast cancer receiving anthracyclines [47]. Another study identified a body mass index ≥ 27 kg/m² as an independent risk factor for long-term cardiac toxicity after anthracycline-based chemotherapy in early breast cancer [19].

CARDIOTOXIC EFFECTS OF CHEMOTHERAPY

Common cardiotoxic manifestations of chemotherapy include left ventricular dysfunction (decrease in cardiac contractile function) and heart failure (clinical syndrome resulting from the inability of the heart to supply sufficient blood flow to meet the body’s needs), myocardial ischemia and infarction, hypertension, and bradycardia. Less frequent manifestations include myocarditis, pericarditis, arrhythmias such as atrial fibrillation, premature atrial contractions, premature ventricular contractions, supraventricular tachycardia and atrial flutter, and QT prolongation. Multiple recent reviews [48–53] have described in detail the pathophysiology, diagnosis, and management of these cardiotoxic manifestations. Data are scarce on the specifics of these complications in elderly women with breast cancer; aspects unique to this population are not well known. Until such data become available, data from studies of all-age and younger adult populations have to be extrapolated to elderly women with breast cancer.

PREVENTION

Risk factors for chemotherapy-related cardiac complications should be assessed in all patients diagnosed with

breast cancer who are being considered for chemotherapy. Patients with significant risk factors should be referred to a cardiologist prior to the start of chemotherapy for further risk stratification and risk modification. Patients should be managed by interdisciplinary teams consisting of oncologists, cardiologists, primary care physicians, geriatricians [54], pharmacists, and nurses. Collaborative assessment by oncologists and cardiologists before the start of chemotherapy can lead to early identification of patients at risk and avoidance or minimization of cardiac complications [49, 55–57]. A lower-intensity chemotherapy regimen should not be chosen simply based on a patient’s risk factors or predisposition for chemotherapy-related cardiac complications.

Drug interactions should be avoided by careful review of the patients’ medications—both prescription and non-prescription [58]. Active involvement of pharmacists in the care of older patients receiving chemotherapy will lead to prevention of medication errors and minimization of drug interactions and subsequent toxicity [59].

Chemotherapy regimens involving the concurrent use of drugs known to synergistically increase the risk for cardiotoxicity should be avoided. For example, the risk for doxorubicin-related cardiotoxicity increases when it is given in combination with paclitaxel, likely secondary to changes in doxorubicin pharmacokinetics from the polyoxyethylated castor oil in the paclitaxel solvent [60]. Another drug known to increase anthracycline-related car-

diotoxicity is trastuzumab. Similarly, the risk for trastuzumab-related cardiotoxicity is increased with the concomitant use of anthracyclines, carboplatin, paclitaxel, and cyclophosphamide [21–23, 61–65].

When considering potentially cardiotoxic drugs, alternative classes of drugs that are equally or more efficacious and less cardiotoxic should be considered [66]. Analogs such as epirubicin [67–71], idarubicin [72, 73], and liposomal-encapsulated doxorubicin [74, 75] are known to confer a lower risk for cardiac complications than doxorubicin. The patient's lifetime cumulative dose should be limited [14, 17]. Certain schedules have been shown to confer a lower risk for cardiac complications—a continuous schedule rather than a bolus schedule for anthracyclines [76–80] and a shorter schedule rather than a longer schedule for trastuzumab [81]. Although the anticancer efficacy of anthracyclines with cardioprotectants has not been well studied in elderly women, when possible, consideration should be given to the use of cardioprotectants such as dexrazoxane to prevent or minimize anthracycline-related cardiotoxicity [82–84]. Medications that may protect against chemotherapy-related cardiac complications include angiotensin-converting enzyme inhibitors [85], carvedilol [86], and lipid-lowering agents [87].

Patients should be counseled about lifestyle changes such as smoking cessation, physical exercise [88], and weight loss that could potentially reduce their risk for cardiovascular complications.

FUTURE DIRECTIONS AND NEEDS

Evidence-based guidelines on the early detection, diagnosis, and management of chemotherapy-related cardiac complications, which can also be applied to older patients with breast cancer and variable cardiovascular risks, are urgently needed. This will be made possible by increasing recruitment of older patients to breast cancer chemotherapy trials and the conduct of clinical trials designed specifically to

study cardiac complications of breast cancer therapy in older women.

Routine monitoring and reporting of cardiovascular complications of treatment should be mandated for all oncology clinical trials involving potentially cardiotoxic agents. Assessment of cardiac complications should become an integral part of phase I trials to allow development of drugs that confer a lower risk.

Establishing the utility of the currently available techniques and biomarkers for the prediction, detection, and prognostication of chemotherapy-related cardiac complications should be a high priority. Newer noninvasive and cost-effective diagnostic tools should be developed for the early identification of preclinical cardiotoxicity and susceptibility to cardiac complications.

CONCLUSIONS

Chemotherapy-related cardiac complications can impact the effectiveness of treatment and the overall prognosis of older patients with breast cancer. Cardiac complications result from complex interactions of multiple pre-existing patient factors, cancer-related factors, and toxic effects of the chemotherapy drugs. Recognition of these factors and collaborative care by oncologists and cardiologists are important for the prevention, early detection, and minimization of cardiac complications. Cardiac complications of breast cancer therapy will likely remain a significant challenge in the future because of the increasing aging population of patients with cancer and the introduction of new cancer treatments.

AUTHOR CONTRIBUTIONS

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