CLINICAL CASE CHALLENGES

Cardiovascular Prevention Strategies in Breast Cancer

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With advances in breast cancer therapy, there has been substantial improvement in cancer-specific prognosis for women with breast cancer. As expected, with greater breast cancer survival, risks for competing causes of death have increased in this group of patients, specifically the risk of cardiovascular disease (CVD). Clinical trial data on pharmacological therapies (e.g., statins) to mitigate the development of CVD in these patients are limited.

A CVD prevention program in the cardio-oncology setting provides an opportunity to review planned or delivered cancer therapies that affect CVD risk, individualize cardioprotective medical treatment for patients with cancer that is based on a combination of exposures and underlying risk factors, and offer services to promote healthy lifestyle choices. In 2016, the MD Anderson Healthy Heart program (MD Anderson Cancer Center, Houston, Texas) was initiated with these goals in mind, understanding that the evidence base for how to treat CVD effectively in patients with cancer is rapidly evolving. In this case review, we illustrate the challenges and opportunities in initiation of pharmaceutical and behavioral interventions for patients with breast cancer who are undergoing active treatment and receiving survivorship care.

CASE 1: STATIN USE

A 56-year-old African-American woman is diagnosed with triple-negative left-sided invasive breast carcinoma. She completed a regimen of dose-dense AC (doxorubicin [Adriamycin, 240 mg/m^2] and cyclophosphamide) and paclitaxel (Taxol) 6 months ago, followed by left segmental mastectomy with sentinel lymph node biopsy and radiation therapy. Her body mass index is 32.1 kg/m^2, and her blood pressure (BP) is 123/74 mm Hg. She denies ever smoking and currently takes lisinopril 5 mg daily for hypertension. Her lipid panel is as follows: total cholesterol, 217 mg/dl; triglycerides, 78 mg/dl; high-density lipoprotein, 53 mg/dl; and low-density lipoprotein (LDL) cholesterol, 148 mg/dl.

The American College of Cardiology (ACC) and American Heart Association (AHA) guideline on the assessment of cardiovascular risk provides the rationale and validation of the pooled cohort equation (PCE) to risk stratify patients for preventive strategies (1). The PCE estimates the 10-year absolute risk of having a first myocardial infarction, a stroke, or death from either a first myocardial infarction or a stroke, and it is based on a set of risk factors. An atherosclerotic CVD (ASCVD) risk score of ≥7.5% over 10 years is considered the threshold for considering statin therapy, with use of moderate- or high-intensity statins dependent on the presence of clinical atherosclerotic disease, diabetes, and/or LDL cholesterol ≥190 mg/dl (2).

In patients with breast cancer, there are several limitations to using the PCE. First, the PCE is a 10-year risk estimate to aid decisions regarding pharmacological therapies; however, treatment exposures (e.g., anthracyclines, radiation) in the breast cancer setting are associated with both short-term (days to months) and long-term (10 to 20 years) CVD events. Second, the PCE has been validated only in individuals age 40 and older, and approximately 7% of breast cancer patients are <40 years old. Finally, the PCE fails to account for the multiplicative impact of traditional CVD risk factors among those patients who receive cardiotoxic treatments. Thus, in breast cancer patients who are <40 years of age and/or have had systemic cardiotoxic treatment, the PCE is insufficient in estimating 10-year ASCVD risk.

The most recent 2018 ACC/AHA guideline on the management of blood cholesterol suggests that additional cardiovascular "risk enhancers" (e.g., chronic kidney disease) should be taken into account when discussing statins with patients (2). These recommendations are supported by the most recent 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease, which advocates for a "team-based care approach" to controlling risk factors associated with ASCVD (3). Although specific breast cancer exposures were not considered "risk enhancers" in either guideline, this brings to light the need to consider the individual's cancer treatment exposures in combination with traditional CVD risk factors to personalize a risk discussion with patients.

PRACTICAL STRATEGIES. First, patients with breast cancer should be screened for lipid disorders and measures of insulin resistance, given that these factors are associated with worse cardiovascular and breast cancer outcomes. In patients with breast cancer between 40 and 75 years of age who have LDL >70 mg/dl and type 2 diabetes or a 10-year ASCVD score ≥7.5%, statin therapy is recommended in addition to lifestyle changes independent of earlier exposures. For those patients with a score <5% (considered low risk), determination of statin use is on a case-by-case basis, given that most of these women are younger (<40 years of age), although they are more likely to have received more aggressive therapies for their cancer on the basis of our experience. In patients with an ASCVD 10-year risk of 5% to <7.5%, we favor initiating statins in those women who have undergone left-sided radiation to the breast. We acknowledge that a recommendation for statins among those women who have received anthracycline-based chemotherapy with or without trastuzumab will require additional clinical trial data (NCT01988571; NCT02096588).

In the case presented here, the patient's 10-year ASCVD risk is 5.1%. Given the patient's earlier left-sided radiation exposure and LDL of 148 mg/dl, the patient was prescribed a moderate-intensity statin, atorvastatin 20 mg daily, after a discussion regarding statins side effects, potential cardiac benefit, and unknown factors regarding use in patients with cancer. Atorvastatin was recommended because it has lipophilic properties that were shown in a meta-analysis to demonstrate antitumor efficacy (4). The patient was advised about lifestyle modification (e.g., physical activity, diet) given the known role of weight loss in the reduction of LDL and the delay in development of type 2 diabetes (3). Implementation of both pharmacological and behavioral strategies for risk factor modification can be facilitated by a cardio-oncology rehabilitation program (5).

CASE 2: ANTIHYPERTENSIVE MEDICATION DURING ACTIVE TREATMENT FOR BREAST CANCER

A 35-year-old white woman is diagnosed with human epidermal growth factor receptor 2–positive right-sided invasive breast carcinoma. She received a neoadjuvant TCH (docetaxel [Taxotere], carboplatin, trastuzumab) regimen and underwent a right-sided mastectomy and sentinel lymph node biopsy. She had residual disease at the time of surgery and was recently started on an adjuvant FAC (fluorouracil, doxorubicin [Adriamycin], and cyclophosphamide) regimen. Her body mass index is 34.5 kg/m², and her BP has been measured at 145/90 mm Hg on 2 separate clinic visits. She is a nonsmoker, is not taking any medications, and has a left ventricular ejection fraction of 60%.

Hypertension is a major risk factor for trastuzumab-induced cardiac dysfunction, and it also worsens the risk for long-term mortality among those patients diagnosed with anthracycline-induced heart failure (6). One approach among women with exposure to trastuzumab and/or anthracyclines is to treat to a more aggressive BP goal (<130/80 mm Hg) regardless of 10-year CVD risk estimates if they are in the midst of treatment or have

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AHA = American Heart Association

ASCVD = atherosclerotic cardiovascular disease

BP = blood pressure

CPET = cardiopulmonary exercise testing

CVD = cardiovascular disease

LDL = low-density lipoprotein

PCE = pooled cohort equation

TABLE 1 Example of a 16-Week Periodic Aerobic Exercise Training Program

Week Numbers (of 16)	Monday	Tuesday	Wednesday	Friday	Saturday
1 and 2					
Duration, min	20	–	20	20	–
Target heart rate, %*	60	–	55	60	–
3 and 4					
Duration, min	30	–	30	20	–
Target heart rate, %*	65	–	55	65	–
5 and 6					
Duration, min	20	30	30	30	–
Target heart rate, %*	70	55	65	55	–
7 and 8					
Duration, min	20	35	35	35	–
Target heart rate, %*	70	55	65	55	–
9 and 10					
Duration, min	20	40	40	40	35
Target heart rate, %*	75	55	65	55	55
11 and 12					
Duration, min	35	45	45	45	45
Target heart rate, %*	75	55	65	65	55
13 and 14					
Duration, min	20	35	35	20	35
Target heart rate, %*	75	55	65	75	55
15 and 16					
Duration, min	25	45	45	25	45
Target heart rate, %*	75	55	65	75	65

*Target heart rate during aerobic exercise is a proportion (%) of peak heart rate assessed during cardiopulmonary exercise testing. For example, an individual who attained a peak heart rate of 170 beats/min will have a target heart rate of 102 beats/min during aerobic exercise at 60% effort.

earlier exposure to anthracyclines, anti–human epidermal growth factor receptor 2 therapy, or both. This approach is supported by the most recent 2017 BP guidelines, which state that in adults at increased risk for heart failure, it is recommended that BP should be <130/80 mm Hg irrespective of 10-year ASCVD risk (7). Large randomized clinical trials will be required to assess whether specific medications for BP control should be used to prevent cardiotoxicity. In the meantime, a focus on aggressive BP targets in the risk discussion with breast cancer patients and survivors should be emphasized.

PRACTICAL STRATEGIES. For this case, the patient was given a BP goal of <130/80 mm Hg and was advised to consider medical therapy during chemotherapy. Lifestyle modifications were also strongly emphasized. The patient declined medical therapy but agreed to maintain a BP log. One month later, the patient's log revealed BP consistently higher than 130/80 mm Hg. She agreed at that time to start lisinopril 5 mg daily. Lisinopril or carvedilol could be considered in this setting given their known effectiveness as antihypertensive agents and their use in preventing cardiotoxicity, according to a small clinical trial (8). Candesartan has also been shown to protect against early declines in left ventricular ejection fraction in this setting (9). Meta-analyses have demonstrated a modest benefit in attenuating left ventricular ejection fraction declines with neurohormonal antagonists (10).

CASE 3: EXERCISE ROUTINE IN OVERWEIGHT AND OBESE PATIENTS RECEIVING HORMONAL THERAPY

A 58-year-old Hispanic woman was diagnosed with estrogen receptor-positive left-sided invasive breast carcinoma. She had a left-sided mastectomy 2 years before her visit and is currently taking hormonal therapy. Her body mass index is 35.8 kg/m², waist circumference is 90 cm, and BP is 125/78 mm Hg. She is a nonsmoker. She is currently taking anastrozole and a multivitamin.

Physical activity guidelines for cancer survivors published by the American Cancer Society recommend at least 150 min of aerobic exercise and at least 2 days of resistance exercise training per week. In overweight or

obese patients, an increase in physical activity to promote weight loss is recommended in addition to dietary changes.

PRACTICAL STRATEGIES. For this case, an aerobic exercise training program was recommended that incorporates moderate-intensity exercise (50% to 70% of maximal heart rate) at higher volumes (~300 min/week). Before initiating this routine, she performed a cardiopulmonary exercise test (CPET). A CPET is a noninvasive test performed using a stationary bicycle or treadmill for exercise, and it involves both electrocardiographic monitoring and measurements of gas exchange (requiring a facemask or mouthpiece). CPET can assess for multiple organ defects (e.g., cardiac, pulmonary, skeletal muscle) and can delineate heart rate training goals to guide exercise prescriptions. In clinics without CPET availability, an estimated training heart rate can be calculated. In this case, her estimated maximal heart rate is 162 beats/min (220 − age), and her initial exercise heart rate goal is ~100 beats/min (60% of 162 beats/min). Given that she had mild joint pain as a result of her aromatase inhibitor treatment, she was started on a combination of walking and water exercise classes building to 45 min of activity per bout. Also incorporated into her aerobic exercise program was a periodic training scheme that has been shown to have favorable effects on cardiorespiratory fitness in cancer patients (11). Periodization is a training technique designed to vary exercise bouts and frequency over the length of the intervention on the basis of heart rate targets and has been associated with higher adherence rates relative to standard programs (Table 1). Importantly, use of a cardio-oncology rehabilitation infrastructure could help facilitate CPET testing and development of individualized exercise prescriptions for patients with breast cancer (5).

CONCLUSIONS

These sample cases provide clear examples of the gaps in current guidelines and the challenges of trying to use the 10-year ASCVD risk calculator in this specialized group of patients. Although a lack of evidence may have limited practice in earlier years, we now have a growing body of evidence and experience regarding preventive strategies, including pharmacologic, and exercise approaches, to mitigate CVD risk in patients with breast cancer. With the advent of cardio-oncology programs across the United States, the possibilities for greater collaboration among oncology, primary care, and cardiology to provide CVD prevention programs to breast cancer survivors are promising.

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