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Review Article

Breast Cancer and the Heart: Burden on the Chest

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ABSTRACT

Breast cancer survivors after successful treatment face various complications in their life. These problems are related to their psycho-social life and/or related to altered body image or may be because of the side effects of breast cancer therapy. Different types of treatment show various hemodynamic/physiological changes on one or more organ/systems. Cardiovascular is the mainly affected system after breast cancer treatment. Radiation-induced heart diseases (RIHD) involve a broad cardiac pathology comprising myocardial fibrosis and cardiomyopathies, pericardial disease, valvular heart diseases, arrhythmias and coronary artery diseases. Chemotherapy induced cardiotoxicity (CIC) affects the morbidity and mortality in breast cancer survivors. Regardless of cancer prognosis; it impacts the quality of life and overall survival with major limitations in life. Conventional diagnostic procedures and biomarkers can be used to detect RIHD and CIC. Cardio-oncology helps in filling the gap between cardiologist and oncologist to reduce the future cardiac risk in survivors.

Key words: Radiotherapy induced heart disease (RIHD), Chemotherapy induced cardiotoxicity (CIC), Modified radical mastectomy (MRM), Ultrasound tissue characterization (UTC), Myocardial fibrosis.

Key messages: Oncologist should be careful at the time of therapy selection; therapy with less cardiac impact therapy with less cardiac impact is preferred. Collaboration is recommended between cardiologist and oncologist for risk stratification, monitoring, and treatment of breast cancer and associated cardiac complications.

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INTRODUCTION

Life is tough after breast cancer in survivors. They have the list of problems affecting their health and health related lifestyle. Breast is an important part of women body which makes their physic complete, has an active role in women's sexual life, psychological satisfaction and to serve motherhood. Female breasts have sexual and social characteristics; the perception of body image and sexual attractiveness. Breast cancer affects the mammary cells, characterized by mass in the breast, in axilla or changes over the breast skin and nipple. Mammography, magnetic resonance imaging (MRI) and other ultrasound facilities can be used to detect breast cancer. Varies genetic and environmental factors, exposure to radiations, sudden hormonal changes and reproductive factors are major risk factors for breast cancer. Age, sex, drugs, and toxins are considered as secondary factors. Breast cancer has various treatment policies based on severity and pathophysiology. Surgical correction, chemotherapy, hormonal replacement therapy and radiation therapy are the different options. Surgery involves modified radical mastectomy (MRM) and breast-conserving surgery (BCS); which is the complete or partial removal of breast.[1] Body image and sexual problems affect the survivor's psycho-social life after surgery because of affected appearance and sexual life. They are dissatisfied with the appearance as they feel less physically attractive, they avoid meeting people, going outside and they are worried of the scar after breast cancer surgery. They are dissatisfied and distressed about sexual life as well they feel sexually embarrassed and bothered by low desire. Radiotherapy, chemotherapy and hormonal replacement therapy even have many side effects on and in the body.[2,3,4] These all affect the various systems of the body including the nervous system, respiratory system, reproductive system and cardiovascular system etc. Aim of this overview is to describe the association between breast cancer treatments and related cardiac complications.

Radiotherapy induced heart diseases

Radiation therapy (RT) and mastectomy are most common cause of pathological changes in the heart after breast cancer in survivors. The majority of the chemotherapy drugs also precipitate to heart diseases. Radiation-induced heart diseases (RIHD) involve a broad cardiac pathology comprising myocardial fibrosis and cardiomyopathies, pericardial disease, valvular heart diseases, arrhythmias and coronary artery diseases. In most of the cases, tissue fibrosis causes RIHD by multiple pathways including cellular, molecular and genetics in both acute and chronic conditions.[5,6,7]

2D echocardiography is preferred non-invasive tool to detect the myocardial damage or any other cardiac chambers functional changes. Early myocardial changes seen in echocardiography due to breast cancer treatment can be used for risk stratification for cardiovascular disease. Ultrasound tissue characterization (UTC) through cyclic variation of integrated backscatter (CVIBS) tracks structural changes and contractility properties of the myocardium. CVIBS found to be more sensitive method than conventional echocardiography in detecting RT induced myocardial changes in breast cancer patients. Other factors like obesity and smoking also affect CVIBS.[8]

RIHDs are the dose dependent to radiation. Dose per fraction, irradiated volume and preexisting cardiac disease also affect the occurrence of irradiation induced cardiac diseases.[9] Less than 2 Gy heart dose doesn't show clinically significant changes in myocardium but higher dose than that shows the larger magnitude in the septum and in posterior wall. Mechanism of RT induced myocardial changes shows inflammatory changes at initial phase followed by the development of fibrosis.[8]

Initially RT cause damage to mesothelial cells lining of peri and epicedium followed by pericarditis within few weeks of the treatment cycle. Late complications of RT affect the primary arteries and small branch vessels. Mechanism evolves slow endothelial cell injury leading to ischemic changes at the microcirculatory level and loss of capillaries followed by progressive myocardial fibrosis. Conduction defects, valvular defects, and sudden cardiac death are secondary effects of RT in breast cancer survivors post several years.[9]

According to Touhinen SS and team; the process takes 40 days after RT initiation. Myocardial mass, LV septal and posterior myocardium thickness had seen increased with mitral inflow changes.[8]

Short term myocardial perfusion defects have seen in single photon emission tomography (SPECT) in left side breast cancer patients after tangential photon beam RT. Defects were clinically significant at 6 months after RT but no major differences have seen at 12 months and 18 months after RT. Left anterior descending (LAD) was most affected area than circumflex (LCX) and right coronary artery (RCA).[10]

Tricuspid annular plane systolic excursion (TAPSE), a parameter to detect global right ventricular function has reduced by the long term radiotherapy for left breast cancer.[11] Decreasing functional capacity of the right ventricle can cause various cardiac complications including RV myocardial infarction, right side heart failure.

Chemotherapy induced cardiotoxicity

Chemotherapy involves the multiple drugs to kill rapidly dividing malignant cells. In the case of breast cancer; targeted therapies also killed the cardiomyocytes which lead to cardiotoxicity.[12]

Chemotherapy induced cardiotoxicity (CIC) also known as the adverse effect of breast cancer treatment is well documented.[13] CIC affects the morbidity and mortality in breast cancer survivors. Regardless of cancer prognosis; it impacts the quality of life and overall survival with major limitations in life.[14] The majority of the chemotherapy drugs because cardio toxicity; anthracycline and trastuzumab have a significant effect on the heart. However, the side effects of molecularly targeted therapies are not yet understood because these are newly available for cancer treatment.[15] Cardio toxicity associated with chemotherapy can range from asymptomatic sub-clinical echocardiographic changes to a life threatening events like congestive heart failure or acute coronary syndrome.[14]

Damage to vessels and heart muscles can be divided into two types, damage Type I and damage Type II. Where damage Type I is irreversible injury because of cytostatic effect of traditional antineoplastic drugs and associated with myocytic death, damage Type II is reversibly altered signalling pathways due to newer anticancer drugs associated with myocardial stunning or cellular hibernation. Damage Type II shows arrhythmias, arterial hypertension and LVD followed by heart failure.[14,16,17]

Acute or sub-acute complications include supraventricular or ventricular arrhythmias, abnormalities in ventricular repolarization and QT-interval changes in the electrocardiogram. Acute coronary syndrome and pericarditis-myocarditis syndrome are also considered as acute onset of cardiotoxicity occurred within 2-4 weeks after termination of chemotherapy. Congestive cardiac failure and severe cardiomyopathies are late onsets within 1 year or after several years of termination of therapy.[14]

Detection of cardiotoxicity at an early stage and its treatment can prevent permanent damage to heart.[13] Age, sex, family history of cardiovascular disease or CHF, personal medical history of dyslipidemia and arrhythmia are associated with the additional risk to RT induced cardiac diseases and CIC.[14]

CIC is a dose dependent process developed pericarditis-myocarditis syndrome in patients already known for cardiac diseases.[9] Chemotherapy drugs tyrosine kinase inhibitors (TKIs), anthracyclines, alkylating agents, and interferon-alfa are found associated with myocardial dysfunction particularly left ventricular dysfunction (LVD).[18] Ischemic heart conditions are noted with 5-fluorouracil (purine analogs), antineoplastic antibiotics and topoisomerase inhibitors.[19,20,21,22,23] Pericarditis is well documented with cyclophosphamide, bleomycin, and cytarabine. In other hand cardiac arrhythmias are associated with an anthracycline and other antineoplastic agents such as imatinib; because of myocardial injury and metabolic changes in the myocardium.[12,24] Cardio toxicity and hypertension are documented with sorafenib and sunitinib (multi target TKIs) and angiogenic agents. Angiogenesis drugs are associated with LVD and CHF too. Bevacizumab; an anti-vascular endothelial growth factor (VEGF) antibody has a broad spectrum of adverse events including hypertension, pulmonary edema, thromboembolism, pulmonary hemorrhage and gastrointestinal bleeding.[25,26,27]

Progressive left ventricular dysfunction followed by chronic heart failure is another condition noted in patients administered anthracyclines. It is related to dose the patient took during her lifetime. Myocardial fibrosis and myocytic hypertrophy leading to endomyocardial thickening and dilated cardiomyopathy followed by the restrictive endomyocardial disease can be an anthracycline induced cardiac injury. This is progressive in nature. The overall incidence of doxorubicin-induced heart failure was noted 2.2%. Doxorubicin therapy increases the incidence of congestive heart failure with the higher dose among the patients already have cardiovascular risk factors. It increases from 3% to 7% when doxorubicin dose increased to 500 mg/m^2 from 400 mg/m^2.[9,28,29]

Stated the doxorubicin induced heart failure in 43 patients. The majority of the patients were died because of CHF and recurrent episodes of cardiac decompensation within 3 months. In the study patients with doxorubicin induced heart failure was well controlled with diuretics and digitalis. Mortality was high in patients who developed class IV dyspnea after 4 weeks of the last dose of doxorubicin. The average dose of doxorubicin given to the patients was 450 mg/m^2.[29]

The definite cause of heart failure and cardiomyopathy is not well known, various strategies are involved in the treatment.[30]

Heart failure mechanism of doxorubicin shows decreased endogenous antioxidants, increased oxidative stress by increased production of free radicals in the myocardium. Hyperlipidemia and apoptosis caused by Adriamycin also involved in heart failure process.[31] This process considered as direct damage to the heart by anthracyclines.[32] Cardio toxic effect of anthracyclines is increased by the trastuzumab administration along with.[33] Probucol, an antioxidant and lipid lowering drug can be used to prevent heart failure occurrence due to doxorubicin.[31]

Chemotherapy initiates blood clotting; a precursor for thromboembolic events, because cancer cells produce a prothrombotic state. Patient with metastatic disease is at higher risk of thromboembolic events.[34]

Hypertension occurrence is associated with VEGF inhibition followed by restricted nitric oxide (NO) production in arterioles and resistance vessels. Restricted NO production initiates vasoconstriction and increased peripheral vascular resistance as well as blood pressure.[35,36,37]

The risk of electrophysiological changes or arrhythmias is higher with antineoplastic agent's use.[38] Arterial fibrillation (AF) is a more common phenomenon of arrhythmias in breast cancer survivors. The incidence of AF is 18.3 % in patients with the cancer history where it is 5.6% in patients without. Mechanism of AF in breast cancer can understand by inflammation as a common factor in both AF and carcinogenesis. Elevated C-reactive proteins levels in serum found to be statistically significant for systemic inflammation in both the conditions. Serum C-protein is not justified as an independent biomarker for AF in cancer patients.[19]

Multi-modal imaging techniques including echocardiography, ultrasound tissue characterization (UTC) are the traditional methods to detect cardiotoxicity. Biochemical markers i.e. cardiac natriuretic peptides and troponins are also used to identify the patient at potential risk of heart disease. Cardiac troponins have high diagnostic efficacy even it is used for detection of the onset of cardiomyopathy 3 months prior. Cardiac biomarkers can detect the acute onset cardiotoxicity as well these are the predictors for late onset cardiac manifestations.[39,40]

Conventional nuclear medicine imaging can be performed as complementary to ECHO to detect RT induced cardiac damage. Evaluation of

left ventricle ejection fraction (LVEF) is found useful in RIHD as well as in CIC.[9]

Coronary angiogram with radionuclides has poor sensitivity and low predictive power to detect subclinical myocardial damage.[41]

Treatment strategies for CIC

Treatment guidelines are available for the better care of cardiotoxicity associated with cancer drugs. Guideline of American College of Cardiology/ American Heart Association and Heart Failure Society of America is recommended at present. Patients are recommended for angiotensin II receptor blockers (ARB) or angiotensin-converting enzyme (ACE) inhibitors with a beta-blocker if not contraindicated.[20]

European Society for Medical Oncology (ESMO) suggests control on cardiovascular risk factors in breast cancer patients. BP control, lowering the lipid levels and smoking cessation is recommended by ESMO.[42,14]

Described the treatment table of chemotherapy associated cardiotoxicity in which ARBs or ACE inhibitors are the first choices of drugs. In heart failure treatment ACE Inhibitors, ARBs or beta blockers are first priority drugs, alone or in combination; to reverse the remodeling, recovery of cardiac functions and to improve overall survival. ACE inhibitors or ARBs prevent proteinuria and restore adequate blood pressure in case of hypertension. ACE inhibitors are recommended alone to prevent the chemotherapy induced cardiomyopathy. Enalapril and carvedilol in combination preserve the left ventricular systolic function. In thromboembolism anticoagulation is recommended with warfarin or low molecular weight heparin (LMWH); it helps in restoring endothelial function.[14,21]

Hormone therapy induced cardiac disease

Hormone-sensitive or hormone dependent breast cancers are probably promoted by estrogen and progesterone in women. Breast tumors with estrogen and/or progesterone receptors presence call hormone receptor positive (HR-positive) tumors where tumors without estrogen and/or progesterone receptors called HR-negative. 70-85% breast cancers are HR-positive. Hormonal therapy is sometimes needed to suppress the estrogen production or estrogen activity to treat HR-positive breast cancers.[43]

Gonadotropin-releasing hormone (GnRH) agonists also called as luteinizing hormone-releasing hormone (LH-RH) agonists' suppress ovarian function to block estrogen production. Goserelin and leuprolide are the FDA approved drugs used to suppress ovarian functions. Selective estrogen receptor modulators (SERMs) i.e. tamoxifen and toremifene control estragon's effect by preventing estrogen binding to receptors.[44]

Cardiac complications induced by breast cancer hormonal therapy in women are very rare and the mechanism is also unclear. In men with prostate cancer; the incidence of cardiac toxicity is even low 0.5-2.5%. Few cases of tamoxifen induced cardiovascular disease are only reported. Any clinical trial doesn't support hormonal therapy induced cardiac manifestations in breast cancer survivors.[45]

Breast cancer surgery induced cardiac complications

We have already discussed the surgery options in the introduction section. MRM and BCS related cardiac complications are unclear yet. Radiotherapy after breast surgery can induce many cardiac problems as described in the section, radiotherapy induced heart diseases. Adjuvant drug therapy after breast surgery also can develop cardiac toxicity.

CONCLUSION

Collaboration is recommended between cardiologist and oncologist for risk stratification, monitoring, and treatment of CIC. Cardio-oncology is an ideal area for research due to higher incidences of breast cancer and cardiac complications due to its treatment. It will fill the gap between cardiologist and oncologist for better treatment of breast cancer and cut down the future cardiac risk in survivors. Development of cardioprotective antineoplastic agents is much needed as adverse effect profile of chemotherapy affects the cardiovascular system in breast cancer survivors.

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CONFLICT OF INTEREST

No conflict of interest from author's side.

ABBREVIATION USED

CIC- Chemotherapy induced cardiotoxicity; **RIHD**- Radiotherapy induced heart disease; **MRM**- Modified radical mastectomy; **UTC**- Ultrasound tissue characterization; **MRI**- Magnetic resonance imaging; **BCS**- Breast-conserving surgery; **RT**- Radiation therapy; **CVIBS**- Cyclic variation of integrated backscatter; **SPECT**- Single photon emission tomography; **LAD**- Left anterior descending; **RCA**- Right coronary artery; **LVD**- Left ventricular dysfunction; **TKIs**- Tyrosine kinase inhibitors; **VEGF**- Vascular endothelial growth factor; **LVEF**- Left ventricle ejection fraction; **CCF/CHF**- Congestive cardiac/heart failure; **NO**- Nitric oxide; **AF**- Arterial fibrillation; **ACE**- Angiotensin-converting enzyme; **ARB**- Angiotensin II receptor blockers; **ESMO**- European Society for Medical Oncology; **LMWH**- Low molecular weight heparin; **HR-positive**- Hormone receptor positive; **GnRH**- Gonadotropin-releasing hormone; **LH-RH**- Luteinizing hormone-releasing hormone; **SERMs**- Selective estrogen receptor modulators

SUMMARY

Chemotherapy induced cardiotoxicity (CIC) affects the morbidity and mortality in breast cancer survivors. Regardless of cancer prognosis; it impacts the quality of life and overall survival with major limitations in life. Oncologist should be careful at the time of therapy selection; therapy with less cardiac impact is preferred. Collaboration is recommended between cardiologist and oncologist for risk stratification, monitoring, and treatment of breast cancer and associated cardiac complications.

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