

The effects of treatment of early breast cancer on the cardiovascular system.

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ABSTRACT: As more women are surviving breast cancer the focus is shifting on the side effects that may hinder their quality of life. The cardiovascular side effects of multimodality therapy such as radiotherapy, chemotherapy and hormone therapy have been known for quite a long time. As we have come to know the mechanisms of action of these therapies we have had a chance to improve treatment through new methods or drugs thus limiting cardiac toxicity in breast cancer treatment.

Key Words: Breast cancer, Cardiac toxicity, Radiotherapy, Chemotherapy.

INTRODUCTION

One in nine women has a lifetime risk of developing breast cancer. With the establishment of breast cancer screening programs and patient education about self examination breast cancer can be detected and managed in its early stages. Improvements and developments in the treatment of breast cancer include the use of breast conserving therapy and radiotherapy instead of radical mastectomy, chemotherapy, monoclonal antibodies and hormone therapy. All these tools have helped decrease the mortality from breast cancer. As more patients are surviving the disease the side effects both long term and short term are becoming more and more of a concern. Research is focused at understanding the mechanism of action and designing ways of improving preventing and monitoring the side effects. Cardiac toxicity from radiotherapy, chemotherapy and use of monoclonal antibodies has been a concern in the treatment of early breast cancer as well as the long term effects of use of hormone therapy.

Text

Studies investigating breast conserving treatment as an

alternative to radical or modified radical mastectomy demonstrated equivalent results in the management of early breast cancer¹. In the early studies however it was noted that in patients undergoing breast conserving surgery and radiotherapy cardiac toxicity was the primary cause of mortality for excess non breast cancer mortality¹. Radiation to the heart causes both acute and chronic symptoms of cardiac toxicity^{2,3}. The acute symptoms include acute pericarditis, pericardial effusion and arrhythmias. The long term effects are constrictive pericarditis and increased atherosclerosis. The risk is greatest with left breast irradiation and radiation involving the internal mammary lymph nodes.

Radiation injures the endothelium of coronary vessels leading to ischemic injury to myocytes. Biopsy findings from autopsies of patients with heart disease who received radiotherapy demonstrate increase fibrosis in the pericardium, myocardium and endocardium and severe atherosclerosis around the proximal ostia of the coronary arteries⁴. The resultant fibrosis leads to diastolic dysfunction.

Radiation induced cardiac toxicity was more prominent in the earlier studies rather than recent studies. This is due to the change in methods and technology used to treat breast cancer patients. Older methods of breast irradiation involved the treatment of large areas of breast, chest wall and regional nodes resulting in irradiation of large volumes of the heart⁹. In addition equipment for treatment and planning lacked the sophistication to delineate and avoid irradiation to normal tissue structures. The old equipment which involved the use of anterior photon beams and Cobalt 60 or orthovoltage therapy exposed greater volumes of the heart to irradiation. In the 1980s the advent and use of tangential fields and megavoltage linear accelerators improved results. In the 1990s CT based 3D conformal treatment planning which allows for the better protection of normal tissue structures was introduced. Further developments include the use of IMRT and free breathing gating to decrease the risk of cardiovascular complications⁶. In addition the internal mammary lymph nodes are not routinely included in the treatment field.

Chemotherapy in the adjuvant setting plays an important role in breast cancer management and anthracyclines and taxanes are central to chemotherapy protocols. Cardiovascular complications can be acute such as pericarditis, myocarditis, left ventricular dysfunction and arrhythmias or long term resulting in congestive heart failure and systolic dysfunction. Taxanes which are used in combination with anthracyclines potentiate this toxicity by interfering with metabolism and excretion. Anthracycline cause type one cardiac toxicity this is a dose dependant irreversible response with characteristic biopsy changes⁷. The mechanism of action is via the induction of oxidative stress resulting in myocyte degeneration which is seen in biopsies as myofibrillar loss and vacuolar degeneration. Risk factors for anthracycline cardiac toxicity include age greater than 70 years of age, high blood pressure, preexisting coronary artery disease, female sex, previous cardiac irradiation and bolus administration⁸. The minimization of anthracycline induced cardiotoxicity can be achieved by infusional rather than bolus administration, giving the less toxic liposomal forms, opting for epirubicin which is less toxic than doxorubicin and limiting maximum dose⁹. There are also some drugs being investigated such as

Dextrazoxane^{10,11} which is an iron chelator that minimizes oxidative stress however it has been shown to lower response rates to therapy due to stabilisation of DNA topoisomerase complexes.

Adjuvant Trastuzumab is given to women positive for EGFR/Her 2 receptor cardiac toxicity. Cardiac toxicity from this drug will present either as symptomatic congestive heart failure or asymptomatic left ventricular ejection decline¹². Cardiac toxicity from Trastuzumab is classified as type two it is reversible and does not produce the ultra structural changes and cell death seen with anthracyclines it rather causes a type of cell dysfunction, in addition cardiac toxicity is not dose dependant⁷. Instead of myocyte death with Trastuzumab there is a change in geometry in contractile proteins which may explain the reversibility of this effect⁴. Stimulation of the Her 2 neu receptor can protect against oxidative stress caused by anthracyclines therefore blockage can potentiate anthracycline induced oxidative damage. Risk factors of Trastuzumab cardiac toxicity include low LVEF prior to initiation of Trastuzumab therapy, cumulative dose of anthracycline, increased age and prior use of antihypertensive. Exclusion criteria from Trastuzumab include preexisting cardiac disease, prior MI, angina, cardiac dysfunction, heart failure, uncontrolled hypertension, and arrhythmia except rate controlled SVT and low LVEF prior to treatment. The prevention of cardiac toxicity is through close monitoring every 3 months up to 9 months of treatment with a new assessment 6 months after treatment with ECHO or MUGA.

The two forms of hormone therapy which may affect the cardiovascular system are Tamoxifen and the newer third generation aromatase inhibitors. It is well known that estrogens have a protective effect on lipid profile therefore the question at hand is whether antiestrogens increase the risk of coronary artery disease¹³. Tamoxifen has mixed agonist and antagonist effect on estrogen receptors and with respect to lipid profile it has a positive effect decreasing total cholesterol and LDL cholesterol levels while increasing triglycerides^{2,14}. Despite this it has another cardiovascular risk due to the fact that it increases the likelihood of thromboembolic events. Aromatase inhibitors are now replacing Tamoxifen as first line therapy in

post menopausal women. Studies reviewing the data from various trials^{15,16,17,18,19} show that unlike Tamoxifen Aromatase inhibitors don't improve lipid profiles however they don't make them worse either.

DISCUSSION

Efforts to understand the underlying mechanisms which lead to cardiac toxicity have allowed the development of methods of minimizing these effects. In the field of radiotherapy these developments are seen through the use of conformal therapies, IMRT and breathe gating which minimize greatly the amount of radiation which is received by organs at risk such as the heart. Although the use of Anthracyclines is still common in breast cancer treatment the availability of liposomal forms the close monitoring of cardiac function as well as cardio protective drugs have helped keep toxicity to a minimum. Close monitoring

of cardiac function also plays an important role when administering Trastuzumab. Studies on the toxicity profiles of the new Aromatase inhibitors have proven their safety with respect to cardiovascular side effects. All these developments have resulted in better safety and improved quality of life in breast cancer patients.

CONCLUSION

Cardiovascular effects of the various breast cancer treatments still remain a problem today however the more we have come to understand the physiological effects of these methods and with the help of newer technologies we can ensure women a good quality of life.

Disclosure

The authors report no conflicts of interest in this work.

Η επίδραση της θεραπείας του πρώιμου καρκίνου του μαστού στο καρδιαγγειακό σύστημα.

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ΠΕΡΙΛΗΨΗ: Σταδιακά περισσότερες γυναίκες επιβιώνουν με νόσο από καρκίνο του μαστού και η ποιότητα ζωής αποτελεί επικεντρωμένο στόχο καθώς αυτή (QOL) διαταράσσεται από τις παρενέργειες των θεραπειών. Για αρκετά χρόνια είναι γνωστή η τοξικότητα του καρδιαγγειακού συστήματος από τις θεραπείες (όπως χημειοθεραπεία, ακτινοθεραπεία, ορμονοθεραπεία και στοχευμένη θεραπεία) που αφορούν τον καρκίνο του μαστού. Καθώς προοδευτικά γνωρίζουμε τους μηχανισμούς δράσης των θεραπειών αυτών, μας δίνεται η δυνατότητα να βελτιώσουμε τα θεραπευτικά σχήματα μέσω νέων μεθόδων και σκευασμάτων με απώτερο στόχο τον περιορισμό της καρδιοτοξικότητας των θεραπειών αυτών.

Λέξεις Κλειδιά: Καρκίνος του στήθους, Καρδιακή τοξικότητα, Ακτινοθεραπεία, Χημειοθεραπεία.

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