Cardiac Toxicity in the New Breast Cancer Survivor: Review of Potential Cardiac Problems in Cured Patients

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Overview: **Anthracyclines and trastuzumab are cardiotoxic, and this population of patients requires careful cardiac monitoring before, during, and after treatment. Concerns have been raised that aromatase inhibitors used in postmenopausal patients with estrogen-receptor–positive or progesterone-receptor–positive tumors may increase the risk of coronary artery disease. Radiation techniques have improved, but radiation of remaining left breast tissue after breast-conserving surgery and left axillary or chest wall radiation may also cause cardiac myotoxicity. This review provides a brief summary of mechanisms of cardiotoxicity and examines what is known about its incidence, detection, and prevention. The optimum duration of trastuzumab therapy remains to be determined, and it may not be necessary to treat with single-agent trastuzumab after completing chemotherapy. It is uncertain whether the long-term incidence of cardiotoxicity will increase in breast cancer survivors who have received trastuzumab. The optimum method and frequency of monitoring and predicting cardiotoxicity is as yet unknown. Trials must be performed of adjuvant infusional doxorubicin, liposomal doxorubicin, and dexrazoxane in the adjuvant setting, ideally in patients who might benefit from trastuzumab or anthracycline but who have cardiac risk factors. Radiotherapy techniques that reduce cardiac dosage, such as respiratory gating and intensity-modulated radiation therapy with multileaf collimators, may further reduce long-term cardiotoxicity.**

ANTHRACYCLINES AND trastuzumab are cardiotoxic,[1] and this population of patients requires careful cardiac monitoring before, during, and after treatment. Concerns have been raised that aromatase inhibitors (AI) used in postmenopausal patients with estrogen receptor (ER)-positive/progesterone receptor (PR)-positive tumors may increase the risk of coronary artery disease.[2] Radiation techniques have improved, but radiation of remaining breast tissue after breast-conserving surgery and axillary or chest wall radiation may also cause cardiac myotoxicity.[3] The authors seek to provide clinicians with a framework within which to reduce both risk of tumor recurrence and long-term cardiac toxicity.

Anthracyclines

Anthracyclines generate free radicals, particularly in the presence of iron.[4] The alcohol metabolites of anthracyclines such as doxorubicinol inhibit mitochondrial iron-pumping proteins, which are theorized to lead to chronic cardiomyopathy.[5] There are three phases of cardiac damage: acute, which manifests as pericarditis or myocarditis days after a first dose and is rare; subacute, which presents within months with symptoms of congestive heart failure (CHF); and late toxicity, which presents years after completion of therapy. The toxicity is dose dependent.[6] Subacute cardiotoxicity is the most well documented and studied of the three forms.

Anthracyclines' infusional regimens are less cardiotoxic.[7] Other anthracyclines such as epirubicin and idarubicin are less cardiotoxic at equimolar doses.[8] The liposomal form of doxorubicin is less cardiotoxic[9] but has not been used in the adjuvant setting (Table 1).

Trastuzumab

Trastuzumab binds to HER2/*neu* and inhibits epidermal growth factor receptor signaling.[10] Functional HER2/*neu* is known to protect against dilated cardiomyopathy.[11] Single-agent trastuzumab rarely causes cardiac dysfunction[12] but is common in patients treated with concurrent anthracyclines.[1] The synergistic cardiotoxicity of concomitant anthracyclines and trastuzumab has led to their sequential use.

The combined analysis of two phase III trials (National Surgical Adjuvant Breast and Bowel Project [NSABP] B-31 and N9831)[13] of concurrent adjuvant trastuzumab and paclitaxel in HER2-positive breast cancer proved that the addition of 1 year of trastuzumab to doxorubicin and cyclophosphamide followed by 3 weekly (NSABP B-31) or weekly (N9831) paclitaxel, respectively, showed a 33% relative reduction in risk of death and a 12% absolute improvement in disease-free survival at 3 years in the trastuzumab group. Trastuzumab started concurrently with paclitaxel in both trials, and there was significant cardiotoxicity in the trastuzumab arms. The Herceptin Adjuvant (HERA) trial[14] of 1 year of sequential trastuzumab after at least four cycles of adjuvant or neoadjuvant chemotherapy demonstrated a disease-free survival advantage of 8.4% at 2 years but no significant improvement in overall survival. The incidence of severe CHF was much lower at 0.5%. The lesser incidence of severe cardiotoxicity in the HERA trial may reflect more time for the myocardium to recover from anthracyclines before the initiation of trastuzumab or taxanes may potentiate the postanthracycline cardiotoxicity of trastuzumab. N9831 contained a third arm of sequential trastuzumab after taxane, and comparisons of this arm with the concurrent one will be help determine the relative cardiotoxicity of the two approaches. The Breast Cancer International

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Table 1. Mechanisms and Types of Cardiotoxicity Associated with Different Therapeutic Modalities

Treatment Modality	Mechanism	Toxicity
Anthracyclines	Free radical generation in cardiac myocytes[4]	Cardiomyopathy[6]
Taxanes	Neuropathy	Arrythmias[16]
Trastuzumab	Inhibits HER2 signaling[10]	Synergistic cardiomyopathy with anthracyclines[1]
Radiation	Free radical generation in intimal cells lining coronary arteries[19]	Coronary artery disease Ischemic cardiomyopathy[20]
Aromatase inhibitors	Raise cholesterol	Increased cardiac events[17]

Research Group trial 006[15] was similar to NSABP B-31 but also included a nonanthracycline arm of docetaxel, carboplatin, and trastuzumab (Table 2).

Taxanes

Paclitaxel causes arrythmias (asymptomatic bradycardia), and during its initial development there was concern about cardiac toxicity. However, it does not appear to have significant single-agent cardiotoxicity, although it may potentiate that of anthracyclines or trastuzumab. The incidence of cardiac adverse effects increases sharply when cumulative doxorubicin doses exceed 360 mg/m^2 when the two drugs are combined concurrently in the metastatic setting.[16]

Hormone Agents

Phase III trials of adjuvant AIs compared with tamoxifen in postmenopausal women showed increased relative risk of cardiac events and hyperlipidemia in the AI arm. In the Arimidex, Tamoxifen, Alone and in Combination trial, adjuvant tamoxifen compared with AI decreased mortality from coronary heart disease.[17] It has been demonstrated that tamoxifen has cardioprotective effects mediated by its partial agonist binding to the ER receptor,[18] and so AIs probably do not increase cardiac risk above placebo.

Radiation

Ionizing radiation generates free radicals that damage nucleic acids and proteins. Radiating the heart causes microscopic changes such as fibrosis, pericarditis and scarring, and worsening of atherosclerosis. Clinically this translates into cardiomyopathy, thickened pericardium, and coronary artery disease.[19] Radiating the left chest wall or residual left breast produces a 2-fold to 3-fold increase in mean cardiac dose when compared with treating a right-sided breast cancer.[20] Radiation of internal mammary nodes using anterior fields delivers a higher dose to a larger volume of myocardium. Patients treated with radiation for local control of left-sided breast cancer have historically had a higher incidence of cardiac problems, but there is evidence that newer techniques that deliver less radiation to the heart are reducing the impact of cancer laterality on radiation-induced cardiac damage.[21]

The risks of lung cancer and cardiac morbidity and mortality must be balanced against the long-term reduction in local recurrence by two-thirds (8.8% vs. 27.2%) and overall survival benefit in patients with node-positive or large tumors.[22]

Table 2. Incidence of CHF in Trials of Adjuvant Trastuzumab for Breast Cancer

Trial	Incidence of CHF in Control Arm (%)	Incidence of CHF in Trastuzumab arm (%)	p
NSABP B-31[27]	0.8	4.1	< 0.001
N-9831[13]	0	2.9	< 0.001
HERA[14]	0.06	1.73	< 0.001
BCIRG 006[15]	0.95	2.34 (AC-TH)	0.016
BCIRG 006[15]	0.95	1.33 (TCH)	0.54

Abbreviations: CHF, congestive heart failure; NSABP, National Surgical Adjuvant Breast and Bowel Project; HERA Herceptin Adjuvant; BCIRG, Breast Cancer International Research Group; AC-TH, doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab; TCH, docetaxel, carboplatin, and trastuzumab.

Cardiac Monitoring

The most established methods of monitoring cardiac function are two-dimensional echocardiography[23] and multigated acquisition scanning.[24] Baseline left ventricular ejection fraction (LVEF) should be established using either of these modalities before initiating anthracycline or trastuzamab. Decline in LVEF during treatment may herald clinical symptoms of heart failure, and consideration should be given to dose reduction or discontinuation of treatment. Right ventricular biopsy gives very accurate information about microscopic changes in heart muscle but is invasive and remains a research tool.[25] Other methods of monitoring cardiotoxicity include serial serum tropinin and brain natriuretic peptide measurements.[26]

Future Directions

The optimum duration of trastuzumab therapy remains to be determined, and it may not be necessary to treat patients with single-agent trastuzumab after completing chemotherapy. It is uncertain whether the long-term incidence of cardiotoxicity will increase in breast cancer survivors who have received trastuzumab. The optimum method and frequency of monitoring and predicting cardiotoxicity is as yet unknown. Trials must be performed of adjuvant infusional doxorubicin, liposomal doxorubicin, and dexrazoxane in the adjuvant setting, ideally in patients who might benefit from trastuzumab or anthracycline but who have cardiac risk factors. Radiotherapy techniques that reduce cardiac dosage, such as respiratory gating and intensity-modulated radiation therapy with multileaf collimators, may further reduce long-term cardiotoxicity.

CONCLUSIONS

The trials demonstrating the utility of adjuvant trastuzumab excluded patients with a low LVEF, heart disease,

and hypertension. The incidence of cardiotoxicity in patients with these risk factors will probably be higher. It is important to monitor LVEF before starting chemotherapy, at its conclusion, and while on trastuzumab.

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