

Cardiac Toxicity in Breast Cancer Survivors: Review of Potential Cardiac Problems

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Abstract As breast cancer survival is increased by the diagnosis of earlier-stage disease and treatments improve, the side effects of cancer treatments, such as cardiotoxicity, remain clinically important. Although physicians have known for 30 years that anthracyclines cause acute and chronic cardiotoxicity, the cardiotoxic effects of radiation therapy, hormonal therapy (including tamoxifen and the aromatase inhibitors), and chemotherapy with taxanes and trastuzumab treatment have emerged more recently. This review examines the cardiac toxicity of adjuvant therapy, monitoring for early changes and existing guidelines for monitoring cardiac function in patients with breast cancer.

As methods for detecting and treating breast cancer improve, survival of breast cancer patients is increasing but the side effects of adjuvant breast cancer therapy, including cardiotoxicity, remain clinically important. A single breast cancer patient may receive anthracyclines, trastuzumab, and radiation therapy before commencing hormonal therapy. We summarize preclinical and clinical data on incidence, monitoring, and management of both acute and chronic cardiac cardiotoxicity in breast cancer survivors. This information should assist clinicians in advising their patients of the risks and benefits of adjuvant treatments. Awareness of cardiac sequelae will help oncologists contribute to their "cured" patients' life long well being during long term follow-up (1).

Definition and Treatment of Chemotherapy-Related Cardiac Dysfunction

Chronic heart failure (CHF) is a clinical syndrome caused by cardiac dysfunction. (2) Left ventricular dysfunction may be systolic, diastolic, or a combination of both. Asymptomatic and symptomatic left ventricular dysfunction are managed with β -blockers and angiotensin-converting enzyme (ACE) inhibitors. Patients who are fluid overloaded benefit from loop diuretics. The percentage of blood expelled from the resting left ventricle with each systolic contraction or left ventricular ejection fraction (LVEF) is a measure of systolic function. Normal LVEF is 50% or more. Left ventricular dysfunction occurs both in patients with decreased and normal ejection

fraction. Left ventricular dysfunction with normal LVEF is commonly called diastolic dysfunction and when accompanied with dyspnea, fatigue, and fluid retention is known as diastolic heart failure.

Anthracyclines are believed to cause immediate damage to myocardial cells by free radical generation, although it may take months or years for this damage to become clinically apparent. Dexrazoxane is used to prevent free radical generation by chelating intracellular iron. ACE inhibitors and β -blockers may delay further expression and slow clinical progression to CHF by limiting ventricular remodeling. These treatments may be of benefit when asymptomatic systolic dysfunction is detected. LVEF decrease during adjuvant therapy may indicate cardiac damage and thus require dose reduction or discontinuation of cardiotoxic medications and initiation of CHF management. The American College of Cardiology recommends initiation of ACE inhibitors for patients with stage A heart failure and other cardiovascular risk factors and the addition of β -blockers to patients with stage B heart failure (3) However, it is not current practice to always commence these medications in patients who have received cardiotoxic chemotherapy and are asymptomatic. We recommend following the ACC guidelines in patients with asymptomatic decline in LVEF, who should be seen by a cardiologist to discuss treatment. There are no randomized trials of ACE inhibitors post-standard adjuvant chemotherapy for breast cancer. However, when 114 patients treated with high-dose chemotherapy who had at least one elevated serum troponin I level value (>0.07 ng/mL sampled immediately after and 12, 24, 36, and 72 h after the end of chemotherapy infusion, repeated each cycle of chemotherapy) were randomized to 1 year of prophylactic enalapril post chemotherapy ($n = 56$) or no treatment ($n = 58$), the enalapril group did not have significant LVEF decline and suffered fewer cardiac events (1 of 56 versus 30 of 58, $P < 0.001$; ref. 4).

Although several classification systems (3, 5) for heart failure severity have been established (Table 1), a recent editorial proposed a new system for chemotherapy-related cardiac dysfunction (6). Type I is caused by anthracyclines, and type II is caused by trastuzumab. Type I seems to have a greater tendency to result in cell death; type II has a greater tendency to be reversible and results in cell dysfunction. However, a

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Table 1. Comparison of five different classifications of cardiotoxicity focusing on CHF

Classification system (reference)	Grade I	Grade II	Grade III	Grade IV
NYHA	No limitation of activities	Mild limitation of activity	Marked limitation of activity	Confined to bed or chair
American College of Cardiology/American Heart Association (3)	Stage A; at high risk but without structural heart disease or symptoms	Stage B; structural heart disease but without signs or symptoms	Stage C; Structural heart disease with prior or current symptoms	Stage D; Refractory CHF requiring specialized interventions
Clinical toxicity criteria, version 2.0*	Asymptomatic decline of resting EF $\geq 10\%$ but $< 20\%$ of baseline value	Asymptomatic but resting EF less than LLN for laboratory or decline of resting EF of $\geq 20\%$ of baseline value; $< 24\%$ SF	CHF responsive to treatment	Severe or refractory CHF or requiring intubation
Common terminology criteria for adverse events version 3.0 [†]	Asymptomatic, resting EF $< 60\%$ - 50% ; SF $< 30\%$ - 24%	Asymptomatic, resting EF $< 50\%$ - 40% ; SF $< 30\%$ - 24%	Symptomatic CHF responsive to intervention; EF $< 40\%$ - 20% ; SF $< 15\%$	Refractory CHF or poorly controlled; EF $< 20\%$, intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated
Cardiac review and evaluation committee (5)	Decline in LVEF of at least 10% to $< 55\%$ without signs or symptoms of CHF	Global decrease in LVEF	Signs or symptoms of CHF	Decline in LVEF of at least 5% to $< 55\%$ with signs or symptoms of CHF

Abbreviations: EF, ejection fraction; LLN, lower limit of normal; SF, shortening fraction.
*Adverse events are cardiovascular (general) and cardiac left ventricular function; http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf.
[†]Adverse events are cardiac general and left ventricular systolic dysfunction; <http://ctep.cancer.gov/forms/CTCAEv3.pdf>.

recent retrospective analysis of breast cancer patients with doxorubicin-induced CHF found that 87% improved with cardiac medications and that combined treatment with β -blockers, ACE inhibitors seemed superior to ACE inhibitors alone (7). Retrospective reviews had initially reported mortality rates of 43% to 59% in patients who developed CHF after anthracycline treatment (8). Retrospective analyses of patients treated with trastuzumab have shown that patients who develop CHF improve with standard medical therapy for heart failure (ACE inhibitors and the Food and Drug Administration–approved β -blockers carvedilol or metoprolol; ref. 9) In a recent study of 38 patients (10), trastuzumab cardiotoxicity resolved on discontinuation of treatment with or without cardiac medications and did not always recur on rechallenge. Whereas this system has not been generally accepted and may not fully acknowledge the clinical reversibility of anthracycline-induced chemotherapy-related cardiac dysfunction, it does highlight differences between anthracycline-induced and trastuzumab-induced cardiotoxicity.

Anthracyclines

Clinical manifestations of anthracycline cardiotoxicity. Risk factors for anthracycline cardiotoxicity include age older than 70 years, hypertension, preexisting coronary artery disease, female sex, and previous cardiac irradiation or previous anthracycline exposure (8, 11). Mediastinal irradiation, even if given many years earlier, is also associated with increased cardiac sensitivity to anthracycline damage (12).

Acute cardiotoxic side effects of anthracyclines include pericarditis and myocarditis (which are rare and may occur during or after the first dose), left ventricular dysfunction, and

arrhythmias (13); delayed effects include CHF, which may manifest many years later (14). Systolic dysfunction is 6% higher in patients treated with adjuvant doxorubicin (8% of patients) than with cyclophosphamide, methotrexate, and fluorouracil (CMF; 2%; ref. 15). After a cumulative doxorubicin dose of 240 mg/m², asymptomatic decline in LVEF is detected by prospective monitoring (16). After a cumulative doxorubicin dose of 400 mg/m², CHF incidence was estimated at 2% initially (8), but more recently, it has been estimated at 5.1% (11). Doxorubicin toxicity is exponentially dose-dependent and increases dramatically when cumulative doses exceed 500 mg/m². Among patients ages 65 years or older, a higher CHF risk was associated with anthracycline chemotherapy than with CMF chemotherapy or no chemotherapy (17). Anthracyclines are less cardiotoxic when given by infusion than as a bolus (18). Dose-dense regimens given weekly or every 2 weeks were not associated with excess cardiotoxicity (19), although follow-up was limited. Less cardiotoxicity may be associated with liposome-administered doxorubicin than doxorubicin given by other methods (20); however, this cardiotoxicity should be evaluated in large adjuvant trials.

At equimolar doses, epirubicin is less cardiotoxic than doxorubicin because lower levels of secondary alcohol metabolites are produced from epirubicin (21). Cumulative epirubicin doses of > 950 mg/m² are associated with an exponential increase in CHF risk (22). Disease-free survival associated with a cumulative epirubicin dose of 600 mg/m² is superior to that of 300 mg/m² (23). After an 8-year follow-up, CHF was diagnosed in 2% of the 85 patients who received a cumulative epirubicin dose of 600 mg/m² but not in any of the 65 patients who received a cumulative dose of 300 mg/m² (24). Patients treated with cumulative epirubicin doses of 360 to 450 mg/m²

had an asymptomatic decline in LVEF and increased expression of brain natriuretic peptide after a 1-year follow-up (25). Little cardiotoxicity was observed with a cumulative epirubicin dose of 300 mg/m² (26). Thus, strategies to prevent anthracycline-induced cardiomyopathy include limiting the total cumulative dose, infusional regimens, use of doxorubicin analogues, such as epirubicin, and novel delivery systems, such as liposomal or nanoparticle-bound doxorubicin.

Prevention of anthracycline-induced cardiotoxicity with dexrazoxane. Dexrazoxane (ICRF 187) is the sole cardioprotective agent proved to decrease anthracycline-induced cardiomyopathy; it is given as a closed ring form and is then metabolized to an open-ring iron-chelating form (27). However, dexrazoxane may interfere with anthracycline chemotherapy because anthracyclines enhance DNA cleavage by topoisomerase II, but the closed ring form of dexrazoxane stabilizes DNA-topoisomerase II complexes (28). Lower response rates have been observed in patients with metastatic breast cancer randomly assigned to receive doxorubicin and dexrazoxane than in those who received doxorubicin and placebo (29). Among doxorubicin-treated metastatic breast cancer patients, dexrazoxane seems equally cardioprotective when given before the first doxorubicin dose or when the cumulative doxorubicin dose exceeds 300 mg/m² (30). Dexrazoxane should also be given to patients who respond to treatment and who may receive high cumulative anthracycline doses. Dexrazoxane is also cardioprotective against epirubicin-induced cardiomyopathy; in a randomized controlled trial with a median cumulative epirubicin dose of 720 mg/m², dexrazoxane treatment lowered the incidence of cardiomyopathy from 23.1% (placebo) to 7.3% (dexrazoxane; ref. 31). Dexrazoxane remains the only approved preventative agent, but other avenues are being explored. Recently a small randomized single-blind placebo-controlled trial reported that prophylactic carvedilol, a β -blocker with antioxidant properties, had cardioprotective effects in patients treated with anthracyclines (32). Pediatric patients who had completed anthracyclines and were then randomized to the ACE inhibitor enalapril had less increase in left ventricular wall strain than patients on placebo. There was an excess of cardiac deaths in the placebo group, which was not statistically significant (33).

Taxanes

Clinical manifestations of taxane cardiotoxicity. Paclitaxel causes acute asymptomatic bradycardia in up to 30% of patients (34). An early series reported a 5% incidence of serious arrhythmias and myocardial infarction, including ventricular tachycardia in 5 of 140 patients (3.6%; ref. 35). However, a larger database found that only 0.1% of patients suffered from serious bradycardias and could not confirm that taxanes increased the frequency of ventricular tachycardia or myocardial infarction (34). Taxanes interfere with the metabolism and excretion of anthracyclines and potentiate anthracycline-induced cardiotoxicity, especially at high, cumulative anthracycline doses. Excess chemotherapy-related cardiac dysfunction has been found among patients with cumulative doxorubicin doses that exceed 360 mg/m², who also received short paclitaxel infusions shortly after doxorubicin treatment (36). Slow infusion of paclitaxel and doxorubicin (37) or increased time (24 h) between doxorubicin and paclitaxel

treatments (38) decreased cardiotoxicity. When combined with paclitaxel, the cumulative doxorubicin dose should not exceed 360 mg/m², and doxorubicin should be given before paclitaxel (36). Combination treatments with epirubicin, and taxane may be less cardiotoxic (39, 40). A cumulative epirubicin dose limit of 990 mg/m² in combination treatments with paclitaxel has been proposed (40). In clinical trials, docetaxel has not been associated with increased cardiotoxicity when combined with doxorubicin or epirubicin.

Adjuvant taxane trials and cardiotoxicity. Modern adjuvant regimens of taxanes apparently do not increase anthracycline cardiotoxicity. A trial comparing doxorubicin (75 mg/m²) followed by CMF with the combination of paclitaxel and doxorubicin (60 mg/m²) followed by CMF found that the incidences of symptomatic cardiac events at 31 months were similar between arms with (0.3% of patients) and without (0.5%) paclitaxel (41). In a randomized controlled trial of three cycles of dose-dense epirubicin followed by three cycles of paclitaxel followed by CMF compared with three cycles of dose-dense epirubicin followed by CMF, no severe cardiotoxicity was observed in either arm (42). Newer paclitaxel formulations, such as nanoparticle albumin-bound paclitaxel, may cause less of an increase in anthracycline cardiotoxicity (43). Thus, cardiotoxicity may be minimized by judicious choice of agents and regimens.

Trastuzumab

Trastuzumab (44) is a humanized monoclonal antibody that binds to the juxtamembrane extracellular portion (45) of the human transmembrane orphan receptor HER2 (ErbB2; ref. 46), which is the product of the *HER2/neu* gene. The exact mechanism of cardiotoxicity of trastuzumab is unclear (47).

Physiologic role of cardiac HER2. Investigating trastuzumab cardiotoxicity has led to a better understanding of cardiac physiology. HER2 is required for cardiac development. HER2 expression is high in the fetal myocardium and is required for the development of ventricular muscle and heart valves (48). Knockout mice with no functional HER2 die *in utero* (49). Conditional knockout mice lacking HER2 only in ventricular cardiomyocytes develop severe dilated cardiomyopathy by 2 months of age (50). Cardiac stress increases the expression of neuregulin, a paracrine peptide messenger that activates HER2 by inducing its phosphorylation; neuregulin is an established marker of cardiac stress (51). Neuregulin heterozygote knockout mice are more vulnerable to doxorubicin-induced CHF (52).

Preclinical data for trastuzumab-induced cardiotoxicity. Although trastuzumab does not prevent HER2-HER3 heterodimerization (53), it may crosslink the receptors, which activate the internal tyrosine kinase domain and lead to their endocytosis (54). Single-agent trastuzumab is toxic to rat myocytes *in vitro* because it induces activation of the mitochondrial apoptosis pathway and the caspase cascade. Doxorubicin treatment of rat myocytes causes disarray of the myofibrils; this myofibrillar disarray is increased by treatment with trastuzumab and decreased by treatment with neuregulin (55). Human patients with CHF have increased levels of serum *HER2*, but its clinical significance is unclear (56).

Trastuzumab cardiotoxicity in patients with metastatic breast cancer. Although initial trials of trastuzumab in metastatic

breast cancer patients did not prospectively assess LVEF, they found that monotherapy was associated with cardiotoxicity in 2% to 4.7% of patients (57, 58). Retrospective analyses estimated the incidence of cardiac dysfunction at 2.6% in patients receiving first-line, single-agent trastuzumab and at 8.5% in those receiving trastuzumab as second-line or third-line therapy (for Cardiac Review and Evaluation Committee definitions, see Table 1; ref. 5, 9). In another trial, cardiac dysfunction occurred in 27% of patients receiving concomitant anthracycline, cyclophosphamide, and trastuzumab; in 8% receiving anthracycline and cyclophosphamide alone; in 13% of patients with earlier anthracycline exposure receiving paclitaxel and trastuzumab; and in 1% receiving paclitaxel alone (59). Patients with cardiac dysfunction who were treated with concomitant doxorubicin and cyclophosphamide (AC) plus trastuzumab were more likely to have New York Heart Association (NYHA) class III or IV CHF (64%) than those treated with concomitant paclitaxel (20%; ref. 59). The synergistic cardiotoxicity of concomitant treatment with anthracyclines and trastuzumab led to their sequential use (60).

Phase III clinical trials of adjuvant trastuzumab. We focus on cardiac side effects rather than efficacy in our discussion of the adjuvant trials. Improvements in disease-free survival and the incidence of NYHA grades III and IV CHF in each trial at latest follow-up are presented in Fig. 1, and cardiac data are presented in Table 2.

Trials of adjuvant trastuzumab incorporated careful monitoring of LVEF and contained protocol stopping rules, typically stopping the study when a 4% excess of cardiac events was detected (61–64). The first 1,000 patients recruited to the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial underwent cardiotoxicity analysis, and those with a normal post-AC LVEF were randomly assigned to receive paclitaxel with or without weekly trastuzumab. Those treated with trastuzumab had 3.3% more cardiac events after 3 years than those treated with paclitaxel alone (65), which was essentially unchanged after 5 years of follow-up (Table 2). Independent risk factors for trastuzumab-associated CHF were post-AC LVEF, age of older than 50 years, and hypertension

medications. In a combined analysis of the North Central Cancer Treatment Group trial N9831 and the NSABP B-31, 6.7% of patients who had completed anthracycline treatment had a lower LVEF or developed cardiac symptoms preventing the initiation of trastuzumab treatment (61). Nearly one third of patients who started trastuzumab discontinued it: 4.7% with symptomatic CHF, 14.2% with confirmed asymptomatic decline in LVEF, and the rest for noncardiac reasons. Among trastuzumab-treated patients, NYHA class III or class IV CHF or death from cardiac events occurred in 4.1% in NSABP B-31 (66) and in 2.5% in North Central Cancer Treatment Group N9831(67). In an early analysis of the North Central Cancer Treatment Group N9831 trial, a trend toward increased risk of trastuzumab-associated cardiac toxicity was associated with increased patient age. Trastuzumab-associated cardiac events were not related to post-AC LVEF. Among patients who initiated trastuzumab treatment after paclitaxel (i.e., taxane), there was one cardiac death and a 2.2% incidence of CHF (68).

The Herceptin Adjuvant trial (62) allowed physicians to choose adjuvant chemotherapy regimens and then randomly assigned patients who completed chemotherapy and radiation therapy to observation or to either 1 or 2 years of trastuzumab given every 3 weeks. Only 20% of patients received taxanes. Severe CHF was rare among patients receiving 1 year of trastuzumab (0.5%); after a 2-year follow-up, the incidence of grade III or grade IV CHF was 0.6% and incidence of grade II CHF was 1.5%, and 3% had a clinically significant decline in asymptomatic LVEF (69). The broader variety of possible pretrastuzumab regimens and the entry criteria of a pretrastuzumab LVEF of $\geq 55\%$ may account for the lower incidence of cardiac end points, as the baseline anthracycline damage may have been less in this trial than in others.

The Breast Cancer International Research Group trial 006 compared the following adjuvant trastuzumab (given weekly during chemotherapy and every 3 weeks thereafter) and chemotherapy combination treatments: AC plus docetaxel (AC-T); AC plus docetaxel and trastuzumab (AC-TH); and docetaxel, carboplatin, and trastuzumab (TCH). In its first

Fig. 1. The incidence of CHF from the Finnish Herceptin Study (FINHER), Herceptin Adjuvant trial (HERA), Breast Cancer International Collaborative Group trial 006 (006) with TCH and AC-TH analyzed separately, the North Central Cancer Treatment Group trial 9831 (N9831), and NSABP B-31 (B-31). CHF control, percentage of the incidence of NYHA grades 3 and 4 CHF in the nontrastuzumab arm; CHF-T, percentage of the incidence of NYHA grades 3 and 4 CHF in trastuzumab arm; DFS, disease-free survival at the time of the last follow up. FINHER, 3 y (64); HERA, 2 y (69), 006, 23 mo (70), N9831, 4 y (67), and B-31, 4 y (66).

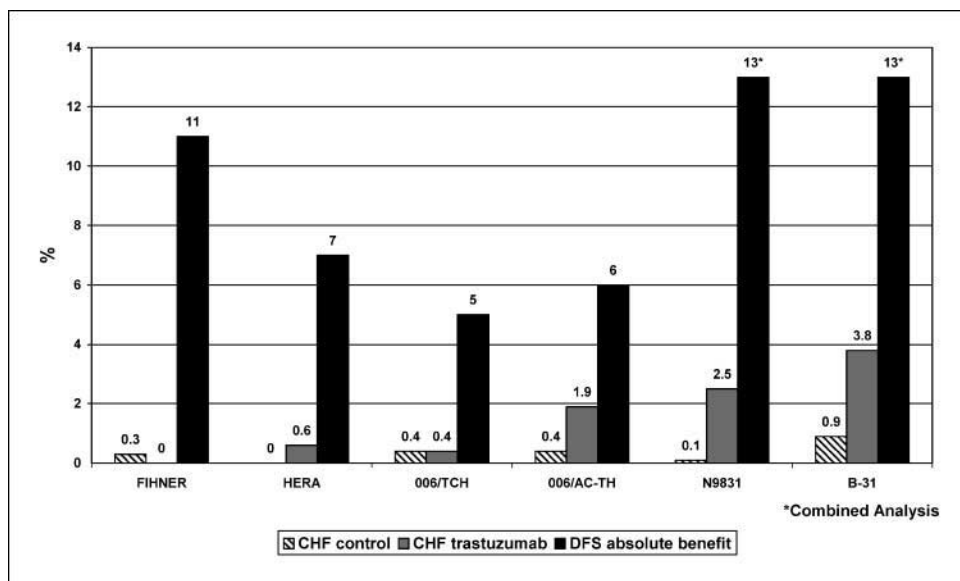


Table 2. Cardiac events and rules for starting, holding, and discontinuing trastuzumab in four adjuvant trials

Trial	No. patients	Events and no. patients	Rule for starting H	Rule for holding H	LVEF evaluation
NSABP B-31 Cardiac safety analysis at 3-y follow-up (61, 65)	Total = 1,664; AC-T arm = 814; AC-TH arm = 850	Asymptomatic decrease in LVEF requiring suspension of H*: data for control arm = NA; H arm = 102 (14%) Cardiac events: control arm = 5 (0.8%); H arm = 31 (4.1%) Cardiac deaths: control arm = 1; H arm = 0 CHF: control arm = 4; H arm = 31 [‡]	Free of cardiac symptoms during AC, post-AC LVEF \geq LLN, and absolute decline \leq 15% Hazard ratio = 5.1	LVEF declines of 10% to 15% and below LLN or \geq 15% absolute fall in LVEF [†] by MUGA	0, 3, 6, 9, 18 mo by MUGA
Cardiac safety analysis at 5-y follow-up (66)	Total = 1845; AC-T arm = 898; AC-TH = 947	Cardiac events: control arm = 6 (0.9%); H arm = 35 (3.8%) Cardiac deaths: control arm = 1; H arm = 0 CHF: control arm = 5; H arm = 35 [‡]	Hazard ratio = 6.6		
N-9831 Initial 3-y follow-up (61, 68)	3 y Total = 1967; AC-T arm = 670; AC-T-H arm = 718; AC-TH arm = 579	Asymptomatic decrease in LVEF requiring suspension of H [§] : control arm = NA; AC-T-Hb arm = 57 (10.8%); AC-TH arm = NA Cardiac events: control arm = 2 (0.3%); AC-T-H arm = 17 (2.5%); AC-TH arm = 20 (3.5%) CHF: control arm = 1; AC-T-H arm = 16; AC-TH arm = 20 Cardiac deaths: control arm = 1; AC-T-H arm = 1; AC-TH arm = 0	Free of cardiac symptoms during AC and post-AC LVEF \geq LLN and absolute decline \leq 15%	LVEF < LLN or 15% absolute fall in LVEF	0, 3, 6, 9, 18 mo by MUGA or ECHO
Updated 3 y follow-up (67)	AC-T arm = 767; AC-TH arm = 875	Updated 3 y follow-up; Cardiac events: control arm = 2 (0.2%), AC-TH arm = 22 (2.5%)			
HERA(62, 69), 2-y follow-up, postadjuvant chemo at discretion of investigator	Total = 3387; observation = 1708; 1-y H = 1678	Decrease in LVEF [¶] : control arm = 9 (0.5%); H arm = 51 (3.0%) Symptomatic CHF ^{**} , including severe CHF ^{††} : control arm = 2 (0.1%); H arm = 36 (2.0%) Severe CHF ^{††} : control arm = 0; H arm = 10 (0.6) Cardiac deaths ^{‡‡} : control arm = 1 (0.1%); H arm = 0	LVEF \geq 55% after all chemo and radiotherapy	LVEF <45% or LVEF <50% and fall >10%	0, 3, 6, 12, 18, 24, 36 mo by MUGA or ECHO
BCIRG 006 (70), 23-mo follow-up	Total = 3174; AC-D arm = 1050; AC-DH arm = 1068; DC*H arm = 1056	Cardiac events ^{§§} : control arm = 10 (0.95%); AC-DH arm = 25; T^C*H arm = 14 Cardiac deaths: none in any arm			0, 3, 6, 9, 18 mo by MUGA or ECHO

(Continued on the following page)

Table 2. Cardiac events and rules for starting, holding, and discontinuing trastuzumab in four adjuvant trials (Cont'd)

Trial	No. patients	Events and no. patients	Rule for starting H	Rule for holding H	LVEF evaluation
FinHer (64), 3-y follow-up	Total = 232	CHF: control arm = 3 (0.3%); AC-DH arm = 17; DC*H arm = 4 Ischemia/infarction: control arm = 0; AC-DH arm = 4; DC*H arm = 1 Arrhythmias: control arm = 7 (0.7%); AC-DH arm = 4; DC*H arm = 9 Decline in LVEF >10%: control arm = 91 (9%); AC-DH arm = 180 (9%); DC*H arm = 82 Decline in LVEF >10%: control arm = 0; H arm = 3 (2.6%) Decline in LVEF <50% or LVEF 15% less than baseline: control arm = 7 (6.0%); H arm = 4 (3.5%) Cardiac infarction: control arm = 1 (0.86%); H arm = 0 Cardiac failure: control arm = 3 (2.6); H arm = 0			Pre-chemo, post-FEC and at 12 and 36 mo after chemo by ECHO or MUGA

NOTE: All trials used the National Cancer Institute's Clinical toxicity criteria version 2.0 except NSABP trial B-31 (65), which used Cardiac Review and Evaluation Committee toxicity criteria (5).
Abbreviations: A, doxorubicin; C, cyclophosphamide; C*, carboplatin; H, trastuzumab; T, paclitaxel; D, docetaxel; CE, cardiac event; HERA, Herceptin Adjuvant trial; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; NA, not available; chemo, chemotherapy.
*A decrease in LVEF of <10% and $\geq 6\%$ less than the LLN or of 10% to 15% and less than the LLN or of $\geq 15\%$.
†Repeat MUGA after 4 wk. If two consecutive holds or total of three holds occur, discontinue trastuzumab treatment.
‡NYHA class III or class IV symptoms with absolute LVEF decrease of $\geq 10\%$ to $\leq 55\%$ or a decrease of >5% to less than the LLN.
§LVEF decrease of $\geq 15\%$ or of <15% and less than the LLN.
|| Patients enrolled before April 25, 2004, with satisfactory post-AC LVEF and completed paclitaxel ($n = 528$).
¶ Absolute decrease of $\geq 10\%$ to an LVEF of <50%.
**CHF was considered symptomatic by a cardiologist and decrease in LVEF of $\geq 10\%$ to <50%.
†† NYHA functional class III or class IV confirmed by cardiologist and decrease in LVEF $\geq 10\%$ to <50%.
‡‡ Death due to CHF, cardiac infarction, documented primary arrhythmia, sudden unexpected death within 24 h of a definite or probable cardiac event.
§§ Clinically significant cardiac events as per independent review panel; Cardiac death or grade 3 or grade 4 toxicities (CHF, cardiac ischemia, cardiac infarction, arrhythmias).

interim analysis (70), symptomatic cardiac events were reported in 0.95% of patients in the AC-T arm, 1.33% in the TCH arm, and 2.3% in the AC-TH arm. Grade III or grade IV CHF was uncommon in AC-T and TCH arms (Table 2 and Fig. 1). Thus, the docetaxel-trastuzumab combination may be less cardiotoxic than the paclitaxel-trastuzumab combination.

A retrospective analysis of Breast Cancer International Research Group trial 006 found that anthracycline-based chemotherapy was associated with increased disease-free survival among patients with HER2-positive tumors that overexpressed topoisomerase II and HER2/neu but not among patients with tumors that only overexpressed HER2/neu (70). Other trials have found similar results (71).

The Finnish Herceptin study randomly assigned 1,010 patients to three cycles of either docetaxel or vinorelbine, followed by three cycles of 5-fluorouracil, epirubicin, and cyclophosphamide (64). The 232 patients with HER2-overexpressing tumors were further randomly assigned as described above to receive nine weekly doses of trastuzumab or placebo during their first three cycles of chemotherapy. This short course of trastuzumab was not associated with LVEF decline or CHF. Use of trastuzumab before epirubicin may have allowed the myocardium to recover from HER2 inhibition before chemotherapy, although trastuzumab, which has a long half-life, may still have been present during anthracycline treatment.

A randomized neoadjuvant trial of 42 patients that compared concomitant trastuzumab and chemotherapy (four cycles of paclitaxel followed by four cycles of FEC75) to chemotherapy alone was stopped before completion of its planned accrual because of an interim analysis that found evidence of improved pathologic complete response in the 23 patients who received trastuzumab (72). Subsequently another 22 patients received neoadjuvant chemotherapy and trastuzumab. A combined analysis showed a 5% decrease in mean LVEF from 65% but no symptomatic cardiac toxicity in the trastuzumab group (73).

Adjuvant trastuzumab summary. To summarize, adjuvant trastuzumab treatment is associated with improved disease-free survival, but it is cardiotoxic, especially when given concomitantly with paclitaxel after AC (Fig. 1). The optimal duration of adjuvant trastuzumab treatment is unknown. If patients must stop trastuzumab treatment because of a declining LVEF, a short course of trastuzumab concomitant with adjuvant chemotherapy still has substantial benefit. Future trials should assess whether patients with tumors that do not overexpress topoisomerase II can avoid anthracycline treatment and thus its cardiotoxicities. Regimens used in the Finnish or Herceptin Adjuvant trials may be beneficial for patients with a high risk of recurrence and low LVEF or patients with multiple cardiac risk factors.

Hormonal Agents

Although estrogen has a positive effect on the lipid profiles of postmenopausal women, it has not been shown to protect against ischemic heart disease (74). Serum levels of some lipid moieties may be associated with higher risk of myocardial infarction in women than men, including low high-density lipoprotein-cholesterol and elevated triglycerides (75). The effects of adjuvant hormonal therapy on lipid profiles have been reviewed elsewhere (76). Tamoxifen has antiestrogenic effects on breast cells and proestrogenic effects on the endometrium and bone, but it has not been shown to protect against ischemic heart disease in large placebo-controlled trials (77) despite earlier metaanalysis which raised this possibility (78). Tamoxifen and other selective estrogen receptor modulators reduce levels of plasma cholesterol (79) and homocystine (80) but increase the level of serum triglyceride (81). Tamoxifen is associated with higher rates of venous thromboembolic disease and stroke than the placebo control (77). Aromatase inhibitors inhibit the conversion of androgens to estradiol in fat and other tissues, including tumors, and thus reduce estrogen levels in plasma and tissue. One large phase III

trial of the aromatase inhibitor letrozole versus tamoxifen reported increased cardiac events in the letrozole arm at a median follow-up of 26 months (82), which persisted in subgroup analysis at 51 months (83). This observation has not been confirmed in trials of other aromatase inhibitors (84). Additional research into the long-term effects of aromatase inhibitors on cardiac disease is required.

Radiation

The most frequently diagnosed cardiac problems during radiotherapy are acute pericarditis, pericardial effusion, and arrhythmias. Acute radiation damage to pericardial and intimal coronary endocytes eventually leads to myocyte ischemia and fibrosis (85). Constrictive pericarditis is a serious long-term complication that may require pericardectomy. It is more frequently seen in patients who receive mediastinal radiation for Hodgkin's lymphoma than those who receive adjuvant tangential breast irradiation. The incidence of constrictive pericarditis with modern techniques is as yet unknown as the median presentation is 13 years postradiation (86). Radiotherapy damage to coronary endocytes triggers inflammation and eventually leads to atherosclerosis (87). The risk of cardiac disease seems to increase for decades after radiation therapy and has been fully reviewed elsewhere (88).

Although an initial metaanalysis of adjuvant breast cancer radiation trials showed that improved disease-free survival was counteracted by excess cardiac mortality (89), a recent metaanalysis that included trials with modern radiation techniques found that increased overall survival was associated with radiotherapy (90). Most cardiac disease has been observed in patients receiving radiation to left chest wall after a left-side mastectomy, but current radiotherapy techniques deliver less radiation to the heart than those of 30 years ago even to patients with left-side tumors (91). Earlier epidemiologic cohort studies observed a higher risk of cardiac death (92) among patients with left-side breast cancer than those with right-side breast cancer, and this risk increased with time since treatment (Table 3). However, a Surveillance Epidemiology End Results analysis (93) of patients who received left-side versus right-side irradiation between 1986 and 1993 did not find significant differences in hospitalization for cardiac disease or heart failure. Although these studies were large and adequately powered, right-side breast irradiation does expose the heart to some radiation, especially if internal mammary lymph nodes are also irradiated. Consequently, a more appropriate control group would have been nonirradiated patients. A recent Dutch study (94) compared 4,414 10-year survivors of breast cancer,

Table 3. Relative risk of cardiac death after radiation for left versus right breast cancer: laterality

Diagnosis	Laterality after diagnosis, RR (95% CI)		
	<10 y	10-14 y	≥15 y
1973-1982	1.2 (1.04-1.38)	1.52 (1.11-1.82)	1.58 (1.29 - 1.95)
1983-1992	1.04 (0.91-1.18)	1.27 (0.99-1.63)	NA
1993-2001	0.96 (0.82-1.12)	NA	NA

NOTE: Data were from ref. 92.

Abbreviations: RR, relative risk; CI, confidence interval; NA, not available.

treated between 1970 and 1986, to the Dutch female population. The authors divided the group into patients treated before and after 1980 when breast-conserving therapy was introduced. Breast irradiation alone did not increase the incidence of cardiovascular disease. Internal left or right mammary chain radiation in the period 1970 to 1979 increased the risk of myocardial infarction and CHF. In the cohort who received internal mammary chain radiation after 1979, the risk of CHF and valvular dysfunction remained elevated but not that of myocardial infarction. Left but not right chest wall irradiation increased the risk of myocardial infarction for the entire treatment period 1979 to 1986. Interestingly patients treated after 1979 who also received adjuvant CMF chemotherapy had an increased risk of CHF compared with those who received radiation alone. Smoking and radiation seemed to have a synergistic effect on increasing the risk of myocardial infarction (94). Patients treated with tangential field irradiation post-left-sided breast conserving surgery had more coronary artery stenosis, especially in the left anterior descending artery than patients with right-sided breast cancer (95). Patients treated with modern techniques that irradiate <5% of heart volume may still develop subtle defects in cardiac perfusion, which could result from irradiation of the left-anterior descending coronary artery causing arteritis (96), but this report was not confirmed in another study (97). Although new techniques, including intensity-modulated radiotherapy (98) combined with free breathing gating (99) and helical tomotherapy (100), may further reduce radiation-induced cardiac toxicities (101), the most important factors in limiting cardiac radiation are associated with the techniques used and the skill of the radiation oncologist.

Cardiac Monitoring

Cardiac monitoring should ideally identify patients at high risk for cardiotoxicity before treatment and patients with asymptomatic toxicity during or after treatment, so that breast cancer treatments can be modified and cardiac medication can be started (102). Cardiac function is usually measured by using echocardiography (ECHO) and multiple-gated acquisition (MUGA), also known as radionuclide angiography (103), to measure resting LVEF. It is important to remember that the two techniques cannot be compared directly and that patients should always be assessed with the same technique when monitoring cardiac changes during treatment. Stressing the myocardium by use of exercise or inotropic agents before measuring LVEF may yield earlier evidence of cardiotoxicity. Another cardiac variable, the early/atrial (E/A) filling ratio, reflects ventricular compliance (i.e., the ability of the ventricle to relax and fill during diastole). Changes in the E/A ratio may predict diastolic dysfunction and so herald a decline in LVEF (104). Diastolic dysfunction seems to be predictive of cardiac morbidity and mortality (105, 106). Whereas resting LVEF is not a perfect measure of cardiac function neither measuring the LVEF during stress nor diastolic function has been prospectively assessed in large adjuvant trials. Trials of adjuvant trastuzumab use the rules for stopping cardiotoxic agents from Schwartz et al. (107). Among 1,487 metastatic breast cancer patients who were monitored by MUGA for 7 years, they identified subset of 282 high-risk patients by one or two of the following three criteria: (a) a decline of 10% or more in absolute LVEF from a

normal baseline to 50% or less, (b) a high cumulative dose of doxorubicin (>450 mg/m²), and/or (c) an abnormal baseline LVEF (<50%). Patients who stopped taking doxorubicin after an LVEF decline were less likely to develop CHF than those who did not.

Cardiac monitoring techniques. MUGA, a nuclear medicine technique, is highly reproducible and able to detect a decline in LVEF in patients treated with anthracyclines, some of whom are symptomatic (107, 108), but it is not able to predict the development or severity of CHF (109). In a retrospective cost-benefit analysis of MUGA among 265 patients, the total cost of all monitoring was less than that for 1 year of care for 15 CHF patients (102). Each scan delivers a dose of 800 mSv, and cumulative radiation exposure limits the suitability of this technique for frequently repeated monitoring.

ECHO is used regularly to monitor LVEF and is more widely available than MUGA. Unlike MUGA, it does not expose patients to ionizing radiation. ECHO was considered prone to operator-dependent variability, but better training and use of automation may overcome intraobserver variation (110). ECHO can accurately measure diastolic function, hemodynamics, and pericardial disease, as well as valvular function, which MUGA is unable to perform.

Endomyocardial right ventricular biopsy via the internal jugular vein, followed by examination of tissue by electron microscopy, provides accurate information on anthracycline-induced microscopic changes in heart muscle (111), but it is invasive, remains a research tool, and is unavailable in most institutions (112). Biopsy specimens from doxorubicin-treated patients have loss of myofibrils, vacuolization of cytoplasm, dilation of sarcoplasmic reticulum, and necrosis (113, 114). Electron microscopy of biopsies from patients with trastuzumab-induced cardiotoxicity does not show the classic Billingham changes of anthracycline exposure but have focal vacuoles, pleomorphic mitochondria, myocardial hypertrophy, and interstitial fibrosis (10, 115).

Serial serum measurements of troponin (T and I isoforms) and atrial natriuretic peptide or brain natriuretic peptide as indicators of cardiotoxicity are under investigation. Elevated troponin I post-high-dose chemotherapy predicted LVEF decline (116). In 703 patients who underwent high-dose chemotherapy, serial troponin I measurements enabled stratification into three groups with different risk for cardiac events in the 3 years postchemotherapy (117). In a prospective trial of patients treated with doxorubicin or epirubicin, elevated serum levels of atrial natriuretic peptide or brain natriuretic peptide did not predict LVEF decline (118). Additional investigation is required before serum monitoring can be recommended outside the setting of a clinical trial. Proteomics has been shown to predict anthracycline-induced cardiotoxicity in animal models (119).

Cardiac magnetic resonance imaging measures many cardiac variables (including LVEF and LV muscle mass) and has little between-test variability and good receiver operating characteristics (120), but it is time consuming and not widely available. Cardiac magnetic resonance imaging is able to assess anthracycline cardiotoxicity (121). Delayed enhancement gadolinium imaging detects myocarditis (122). Because of its high reproducibility, use of cardiac magnetic resonance imaging in clinical trials could lower the number of patients necessary to reliably evaluate the cardiotoxicity of new agents.

Decreased uptake of radiolabeled metaiodobenzylguanidine, an analogue of norepinephrine, is associated with damage to cardiac sympathetic nerves and with cumulative doxorubicin dose in rat models (123). Metaiodobenzylguanidine scintigraphy, a method to measure uptake of radiolabeled metaiodobenzylguanidine, seems to detect Adriamycin-induced cardiomyopathy (124) but has not been widely accepted.

Radiolabeled antimyosin antibodies may be useful in diagnosing cardiac dysfunction and predicting toxicity. When cardiac myocytes are damaged, myosin is exposed and can be detected by antimyosin antibodies. Immunoscintigraphy compares the heart-to-lung ratio uptake of indium-radiolabeled antimyosin antibodies. When LVEF measured by MUGA was compared with antimyosin immunoscintigraphy in patients who had been treated with high cumulative epirubicin doses, an increase in the heart-to-lung ratio preceded a decline in the LVEF (125). Antimyosin immunoscintigraphy may also predict severe cardiotoxicity at low doxorubicin doses (126). Although this technique seems to be very sensitive, it may lack the specificity to predict which patients should stop treatment (127). A report of myocardial uptake of radiolabeled trastuzumab predicting subsequent chemotherapy-related cardiac dysfunction (128) has not been confirmed (129).

Our recommendations for cardiac monitoring. Patients treated with adjuvant trastuzumab should have LVEF assessed by ECHO or MUGA at baseline after completing anthracycline treatment, and while on trastuzumab at 3-month intervals, or sooner, if CHF symptoms develop. Clinicians should use the same rules for stopping trastuzumab as the trial in which the regimen was described (Table 2). We recommend holding trastuzumab treatment when an asymptomatic absolute decline in LVEF below the lower limit of normal is detected. If LVEF improves on subsequent reassessments, trastuzumab treatment

may be restarted. We do not recommend routine monitoring of unproved serum markers, such as troponin or brain natriuretic peptide outside a research setting. Cardiac magnetic resonance imaging has good receiver operating characteristics and reliability and should be considered for use in phases I and II trials of potentially cardiotoxic agents because changes in a small number of patients are likely to be statistically significant.

Conclusions

Close monitoring of cardiac function in trials of adjuvant trastuzumab has provided new data on the cardiotoxicity of conventional cytotoxic agents. These data indicate that long-term follow-up of cardiac function for breast cancer survivors is required, particularly for those who have received adjuvant radiotherapy and anthracyclines. Symptomatic patients will derive benefit from ACE inhibitors and β -blockers. It is uncertain whether these drugs will help patients with asymptomatic LVEF decline. Because adjuvant trastuzumab trials have excluded patients with cardiac risk factors, there may be a higher incidence of cardiac events when trastuzumab is used in less healthy patients. We recommend following LVEF by use of either MUGA or ECHO before, during, and after trastuzumab treatment. Trials of adjuvant infusional doxorubicin or liposomal doxorubicin should include patients with cardiac risk factors and prospectively study new methods of monitoring and treating cardiotoxicity. Newer radiotherapy techniques may further reduce long-term cardiotoxicity, but recent retrospective reviews suggest that current techniques are less toxic than those used two decades ago. Finally, molecular diagnostics holds promise in identifying patients who do not require anthracyclines or any adjuvant cytotoxic therapy, but this remains to be proved prospectively.

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