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ORIGINAL REPORT

Assessment of Cardiac Dysfunction in a Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Paclitaxel, With or Without Trastuzumab As Adjuvant Therapy in Node-Positive, Human Epidermal Growth Factor Receptor 2–Overexpressing Breast Cancer: NSABP B-31

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ABSTRACT

Purpose

Trastuzumab is effective in treating human epidermal growth factor receptor 2 (HER2)–positive breast cancer, but it increases frequency of cardiac dysfunction (CD) when used with or after anthracyclines.

Patients and Methods

National Surgical Adjuvant Breast and Bowel Project trial B-31 compared doxorubicin and cyclophosphamide (AC) followed by paclitaxel with AC followed by paclitaxel plus 52 weeks of trastuzumab beginning concurrently with paclitaxel in patients with node-positive, HER2-positive breast cancer. Initiation of trastuzumab required normal post-AC left ventricular ejection fraction (LVEF) on multiple-gated acquisition scan. If symptoms suggestive of congestive heart failure (CHF) developed, source documents were blindly reviewed by an independent panel of cardiologists to determine whether criteria were met for a cardiac event (CE), which was defined as New York Heart Association class III or IV CHF or possible/probable cardiac death. Frequencies of CEs were compared between arms.

Results

Among patients with normal post-AC LVEF who began post-AC treatment, five of 814 control patients subsequently had confirmed CEs (four CHFs and one cardiac death) compared with 31 of 850 trastuzumab-treated patients (31 CHFs and no cardiac deaths). The difference in cumulative incidence at 3 years was 3.3% (4.1% for trastuzumab-treated patients minus 0.8% for control patients; 95% CI, 1.7% to 4.9%). Twenty-seven of the 31 patients in the trastuzumab arm have been followed for ≥ 6 months after diagnosis of a CE; 26 were asymptomatic at last assessment, and 18 remained on cardiac medication. CHFs were more frequent in older patients and patients with marginal post-AC LVEF. Fourteen percent of patients discontinued trastuzumab because of asymptomatic decreases in LVEF; 4% discontinued trastuzumab because of symptomatic cardiotoxicity.

Conclusion

Administering trastuzumab with paclitaxel after AC increases incidence of CHF and lesser CD. Potential cardiotoxicity should be carefully considered when discussing benefits and risks of this therapy.

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INTRODUCTION

Trastuzumab (Herceptin; Genentech, South San Francisco, CA) is a humanized monoclonal antibody targeting the extracellular domain of the human epidermal growth factor receptor 2 (HER2) protein. Amplification or overexpression of HER2 is seen in

approximately 25% of invasive breast cancers and is associated with unfavorable prognosis.[1] Trastuzumab was approved for treatment of HER2-positive metastatic breast cancer in 1998 based on improved outcomes in the pivotal trial that evaluated trastuzumab in combination with chemotherapy. However, an increased incidence of cardiac dysfunction (CD) was observed, particularly when trastuzumab was combined with doxorubicin/cyclophosphamide (AC).[2]

As part of the process of filing for US Food and Drug Administration approval for use in metastatic breast cancer, an independent Cardiac Review and Evaluation Committee (CREC) was convened to review the cardiotoxicity data from all metastatic disease trials evaluating trastuzumab and established the following criteria for diagnosis of CD: (1) cardiomyopathy characterized by a global decrease in left ventricular ejection fraction (LVEF); (2) signs or symptoms of congestive heart failure (CHF); (3) decline in LVEF of at least 5% to less than 55% with signs or symptoms of CHF or decline in LVEF of at least 10% to less than 55% without signs or symptoms of CHF. Episodes of CD were characterized according to the New York Heart Association (NYHA) functional classification.[3] AC alone was associated with an overall rate of CD of 8.1% and a class III or IV rate of 3.7%. Addition of trastuzumab to AC was associated with an increase in overall CD rate to 27.3% and an increase in the rate of class III or IV CD to 16.1%. Administration of trastuzumab with paclitaxel in patients with prior anthracycline exposure resulted in an overall CD rate of 13.2% but a class III/IV rate of only 2.2%. The CREC also reviewed patients after treatment for CD when possible. Of 34 patients who developed CD on AC plus trastuzumab, seven had persistent class III or IV symptoms on follow-up compared with 0 of 10 patients who developed CD on paclitaxel plus trastuzumab.[3]

The pivotal trial results justified evaluating trastuzumab with chemotherapy in the HER2-positive adjuvant patient population. This required a trial design that would minimize risk and evaluate the incidence, severity, and reversibility of CD. The low rate and apparent reversibility of class III or IV CHF that was observed when trastuzumab was combined with paclitaxel supported the comparison of AC followed by paclitaxel ± trastuzumab.

Therefore, National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-31 included two stages, with assessment of CD as the primary aim of the first stage. Stage 1 included the first 1,000 patients who received post-AC treatment and were evaluable for cardiac assessment. After favorable review of the stage 1 cardiac data by an independent data monitoring committee (DMC), accrual was extended to the second stage to enroll an additional 1,700 patients. A recent planned joint interim analysis of B-31 and North Central Cancer Treatment Group (NCCTG) N9831 demonstrated a 52% reduction in hazard of first events (recurrence, second primary, or death; hazard ratio [HR] = 0.48; 95% CI, 0.39 to 0.59; $P = 2 \times 10^{-12}$) and a 33% reduction in hazard of mortality (HR = 0.67; 95% CI, 0.48 to 0.93; $P = .015$), prompting the DMCs of both groups to recommend disclosure.[4] We report here the detailed cardiac safety data from B-31 as of that analysis.

PATIENTS AND METHODS

Patient Eligibility and Entry Procedures

Patients must have had histologically node-positive HER2-positive primary breast cancer without evidence of metastatic disease and must have completed primary surgery and axillary dissection. LVEF on multiple-gated acquisition (MUGA) scan had to be ≥ the lower limit of normal (LLN). Patients with active cardiac disease, including angina pectoris or cardiac arrhythmia requiring medication, severe conduction abnormalities, clinically significant valvular disease, cardiomegaly, ventricular hypertrophy, or poorly controlled hypertension, were ineligible. Patients with prior myocardial infarction, CHF, or other cardiomyopathy were also excluded. Protocol approval by the local human investigations committee or IRB was required, with an assurance filed with the Department of Health and Human Services. Written informed consent was required.

Protocol Treatment Regimens

Regimens consisted of either doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 21 days for four cycles followed by paclitaxel (175 mg/m^2) every 3 weeks for four cycles (arm 1) or the same chemotherapy plus weekly trastuzumab starting with the first dose of paclitaxel at a loading dose of 4 mg/kg followed by 2 mg/kg for 51 weeks (arm 2). (Subsequent to May 16, 2003, paclitaxel could be administered weekly at 80 mg/m^2 for 12 weeks.) Patients with lumpectomies received breast irradiation after chemotherapy. Postlumpectomy regional and postmastectomy locoregional irradiation were optional. Trastuzumab was continued during radiation. Radiation of internal mammary nodes was prohibited. Women with hormone receptor–positive tumors were to receive tamoxifen for 5 years.

Cardiac Monitoring

Cardiac history forms were to be submitted at entry, every 6 months for the first 5 years, and yearly thereafter. MUGA scans were required in both treatment arms before entry, after AC, and at 6, 9, and 18 months. Additional scans could be performed at investigator discretion.

Initiation of Trastuzumab and Treatment Discontinuation

Trastuzumab was initiated in arm 2 patients if they remained without cardiac symptoms after AC and their LVEF remained ≥ LLN and had not decreased by more than 15 percentage points from the pre-entry level. Criteria were established for holding trastuzumab in asymptomatic patients if 6- and 9-month LVEF values did not remain within predefined limits, as listed in Table 1. If a participant's LVEF did not meet criteria for continuing trastuzumab, the drug was held for 4 weeks. If a repeat LVEF did not meet criteria for continuation, further administration was prohibited.

Monitoring and Review of Symptomatic CD

We will use the term CHF to denote NYHA class III or IV CD. Patients with lesser dysfunction are not referred to as having

Table 1. Protocol B-31 Rules for Suspension of Trastuzumab

Relationship of LVEF to the LLN	Asymptomatic Decrease in LVEF From Baseline		
	Decrease of < 10 Percentage Points	Decrease of 10 to 15 Percentage Points	Decrease of ≥ 15 Percentage Points
Within radiology facility's normal limits	Continue trastuzumab	Continue trastuzumab	Hold trastuzumab and repeat MUGA after 4 weeks
1 to 5 percentage points below the LLN	Continue trastuzumab	Hold trastuzumab and repeat MUGA after 4 weeks	Hold trastuzumab and repeat MUGA after 4 weeks
≥ 6 percentage points below the LLN	Continue trastuzumab and repeat MUGA after 4 weeks	Hold trastuzumab and repeat MUGA after 4 weeks	Hold trastuzumab and repeat MUGA after 4 weeks

Abbreviations: LVEF, left ventricular ejection fraction; LLN, lower limit of normal; MUGA, multiple-gated aquisition scan.

experienced CHF, although that term is sometimes used to refer to lesser degrees of CD in routine clinical practice.

All symptoms suggestive of CHF were reported within 14 days. Source documents were blinded to treatment arm and reviewed by an independent Cardiac Review Panel consisting of three cardiologists who determined by majority vote whether each patient met prospectively defined criteria for CHF. Criteria mirrored the CREC criteria as follows: NYHA class III or IV symptoms with either a decrease from baseline in LVEF of more than 10 percentage points to less than 55% or a decrease of more than 5 percentage points to less than the LLN. Class III is characterized by symptoms of dyspnea with activities such as climbing a flight of stairs, whereas class IV symptoms are present at rest.

Patients for whom potential CD was reported continued to be monitored by MUGA scans and cardiac follow-up forms that summarized ongoing symptoms and cardiac medications.

Formal Interim Analysis of Cardiotoxicity

The primary cardiac safety end point was the difference in incidence of cardiac events (CE) between arms, defined as confirmed class III or IV CHF or possible/probable cardiac death. During study planning, it was judged that at least a 25% reduction in hazard of mortality was not unlikely with this treatment. This translates to an 8% absolute survival benefit at 10 years (70% *v* 62%). Given this level of expected benefit, there was agreement that a difference in incidence of CE of up to 4% would be acceptable to allow completion of accrual in stage 2. Cardiac interim analyses were scheduled after 200, 600, and 1,000 v patients had been followed for at least 6 months after the first day of treatment with paclitaxel ± trastuzumab. If at any interim analysis the difference in CE occurrence was statistically greater than 4% (one-sided $P < .05$), accrual was to be suspended. Otherwise, accrual would continue to a target of 2,700 patients to assess efficacy. This interim analysis plan had a 12% probability of terminating accrual if the true difference in event rate was 4% and an 85% probability of terminating accrual if the difference was 7%.

Statistical Methods

This report is based on all patients accrued as of February 15, 2005 and all cardiac follow-up data received by April 21, 2005. Primary comparisons are based on the cohort of patients who completed AC and began post-AC treatment with paclitaxel (arm 1) or trastuzumab plus paclitaxel (arm 2). To ensure comparability, all patients in both arms of this evaluable cohort were required to meet the protocol conditions for initiating trastuzumab that were required of arm 2 patients (ie, patients were without cardiac symptoms after AC and had a post-AC LVEF ≥ LLN with a ≤ 15 percentage points decline from baseline). Patients in this cohort were considered to be at risk for CE from day 1 of cycle 5 until recurrence, diagnosis of second primary cancer, or last follow-up. Cumulative incidence was estimated nonparametrically.[5] The difference in cumulative incidence of CE in evaluable arm 1 and arm 2 patients 3 years after day 1 of cycle 5 was compared with the hypothesized difference of 4% using a one-sided 0.05-level test. The ratio of crude hazards for CE was estimated by fitting a Cox model. Secondary intent-to-treat analyses were performed using the cohort of all patients with cardiac follow-up.

Association of risk factors with CE was tested using univariate log-rank analysis. A permutation method was used to compute *P* values.[6] In exploratory analyses, Cox models were fit to assess the independence of predictors. Changes in LVEF from baseline were tested using the signed rank procedure; comparisons of LVEF between arms were tested using the rank sum test applied to changes from baseline.

RESULTS

Accrual and Patient Characteristics

The trial opened on February 21, 2000. Cardiotoxicity interim analyses were reviewed by the DMC on October 1, 2001, October 11, 2002, and October 10, 2003. In all three analyses, the difference in CE rates was less than 4%, so patient accrual continued.[7] By February 15, 2005, 2,043 patients had been enrolled. Figure 1 summarizes their treatment, evaluation, and follow-up. Twenty-two patients refused protocol therapy; AC treatment information is pending for 49 patients; 148 patients did not meet the post-AC cardiac criteria for initiation of trastuzuma and were excluded from the primary cardiac safety analysis, regardless of assigned treatment arm; 36 patients had pending post-AC MUGA scans; and 124 patients did not begin post-AC therapy or had no post-AC follow-up as of this report. The remaining 1,664 patients (81%) are included in the evaluable cohort. The median follow-up of patients in the evaluable cohort is 27 months from the first day of cycle 5. Characteristics of evaluable patients are balanced by treatment arm. Fifty-one percent of patients were ≤ 49 years old at entry, 33% were 50 to 59 years old, and 16% were ≥ 60 years old. Eighty-four percent of patients were

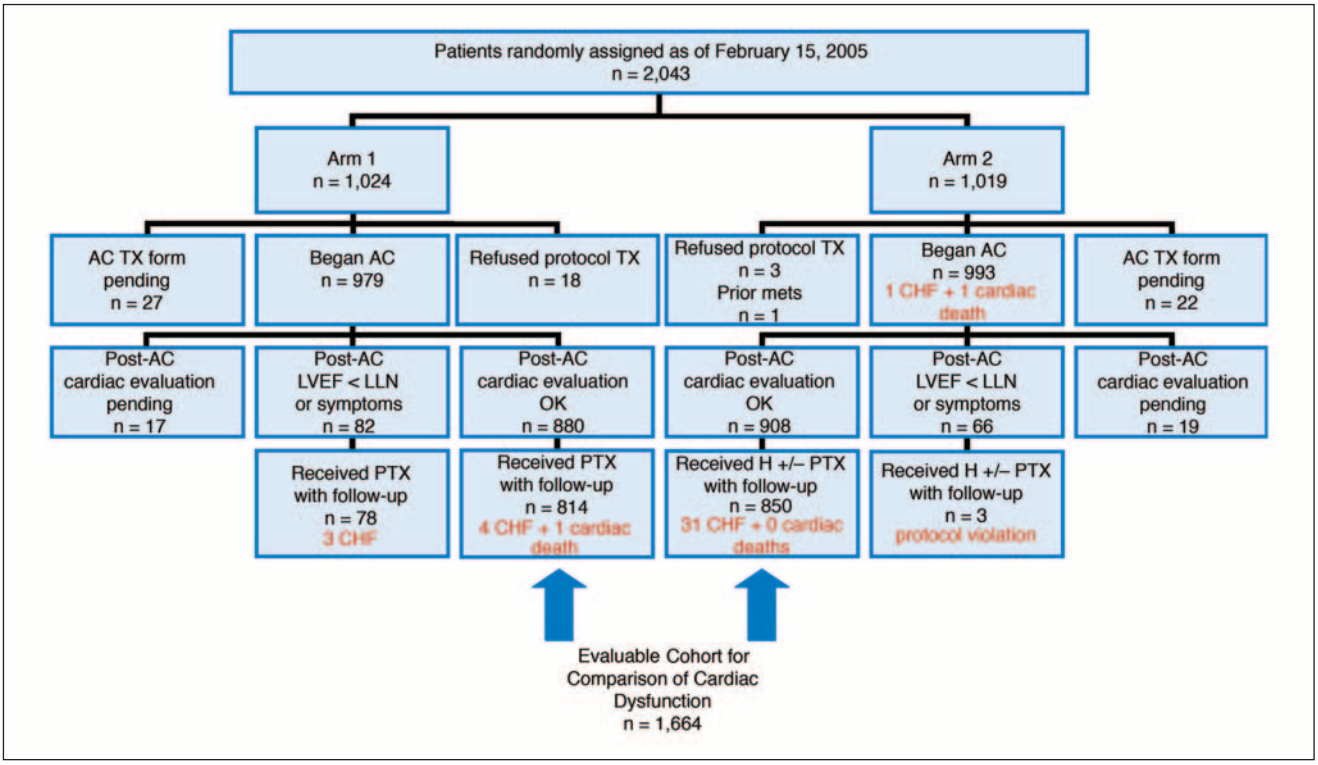


Fig 1. Flowchart of cardiac follow-up and events (arm 1 = doxorubicin and cyclophosphamide [AC] followed by paclitaxel [PTX]; arm 2 = AC followed by PTX plus trastuzumab [H]). The evaluable cohort (n = 1,664) is defined as all patients completing AC without cardiac symptoms, having a satisfactory post-AC multiple-gated acquisition scan, and beginning treatment with PTX ± H. TX, treatment; Mets, metastases; LVEF, left ventricular ejection fraction; LLN, lower limit of normal; CHF, congestive heart failure.

white, 8% were black, and 8% were of other or unknown race/ethnicity. Fifty-seven percent of patients had one to three positive nodes, 29% had four to nine positive nodes, and 14% had ≥ 10 positive nodes. Fifty-nine percent of patients had a pathologic tumor size of more than 2.0 cm. Fifty-two percent of patients had estrogen receptor–positive tumors.

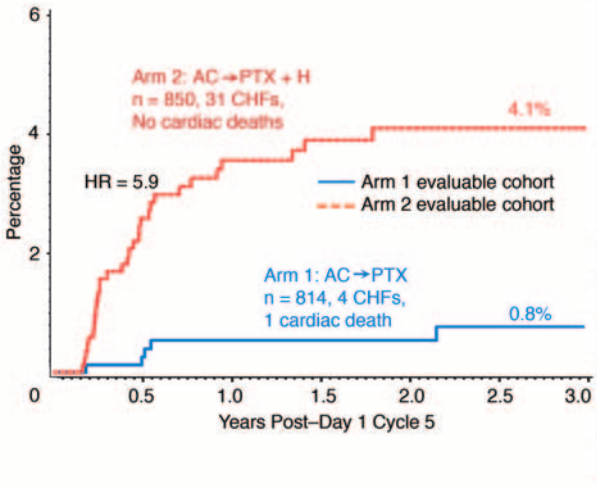
Cumulative Incidence of CEs

Among 814 evaluable control patients, five met criteria for a CE (four CHFs and one probable cardiac death). In the arm 2 evaluable cohort, 31 of 850 patients experienced a CE (31 CHFs and no cardiac deaths). Cumulative incidence of CEs in the control arm 3 years after day 1 of cycle 5 was 0.8% (95% CI, 0.3% to 1.9%). Among trastuzumab-treated evaluable patients, the cumulative incidence of CEs 3 years after day 1 of cycle 5 was 4.1% (95% CI, 2.9% to 5.8%; Fig 2). The difference between the arms was 3.3% (95% CI, 1.7% to 4.9%), which was in agreement with the 4% anticipated increase ($P > .5$). The relative risk of a CE was 5.9 in trastuzumab patients versus control patients (95% CI, 2.3 to 15.3; $P < .0001$). Three of the 31 cases of CHF in arm 2 occurred more than 1 year after initiation of trastuzumab.

Five additional CEs occurred in patients not included in the evaluable cohort (three patients in arm 1 and two in arm 2; Fig 1). In arm 2, a patient died of CHF after her third cycle of AC. A second patient with multiple cardiac risk factors died of cardiopulmonary collapse after her first dose of AC. Neither patient received paclitaxel or trastuzumab. In arm 1, three patients with post-AC LVEF less than LLN received paclitaxel and subsequently experienced CHF. (These patients were not protocol violations because normal post-AC LVEF was not required to initiate paclitaxel, although it was required in arm 2 patients to receive trastuzumab.) The intent-to-treat 3-year cumulative incidence of CEs in all arm 1 patients was 1.1% (95% CI, 0.6% to 2.3%) compared with 3.9% in the entire arm 2 cohort (95% CI, 2.8% to 5.5%).

Recovery of Cardiac Function After CHF

Among the 31 evaluable patients meeting criteria for CHF who received trastuzumab, none have died for reasons other than metastatic breast cancer. Twenty-seven of the 31 patients have been followed for ≥ 6 months after diagnosis of CHF, of whom 26 have been without symptoms of CD for at least 6 months. However, 18 patients continued to receive cardiac medications (Table 2). Twenty-four of the 27 patients have reported LVEF assessments ≥ 6 months after the diagnosis of their CHF, and of these 24 patients, 17 had decreased LVEF relative to baseline at their last available MUGA. The most recent LVEF values were between 40% and 69% in all except one patient whose LVEF was



Years Post–Day 1 Cycle 5	Cum Inc Arm 1 (%)	Cum Inc Arm 2 (%)	No. at Risk
0.5	0.3	2.6	1,472
1.0	0.5	3.6	1,202
1.5	0.5	3.9	983
2.0	0.5	4.1	775
2.5	0.8	4.1	595
3.0	0.8	4.1	405

Fig 2. Cumulative incidence (Cum Inc) of cardiac events (congestive heart failure [CHF] or possible cardiac death) in evaluable cohort (arm 1 = doxorubicin and cyclophosphamide [AC] followed by paclitaxel [PTX]; arm 2 = AC followed by PTX plus trastuzumab [H]). Evaluable patients completed AC with a satisfactory post-AC multiple-gated acquisition scan, had no cardiac symptoms, and began treatment with PTX ± H. Time origin is day 1 of cycle 5.

25% (Fig 3B). Of the five confirmed patients with CHF in arm 1, three have died (probable cardiac death, metastatic breast cancer, emphysema). One of the two surviving patients has been followed for ≥ 6 months after her diagnosis of CHF and is currently symptomatic and receiving medications (Table 2).

Recovery of Cardiac Function in Patients With Symptoms of Possible CD That Did Not Meet Criteria for CE

In addition to those patients with confirmed CHF, 43 evaluable arm 2 patients reported symptoms of CD that did not meet protocol criteria for a CE. Thirty-nine patients have been followed for ≥ 6 months since onset of symptoms, of whom one patient reported symptoms of CD at last follow-up; eight patients continued to receive cardiac medication (Table 2). MUGA results have been reported ≥ 6 months after onset of symptoms for 30 of the 39 patients. Current LVEF results range from 45% to 86%, except for one patient whose LVEF was 40% (Fig 3D). Twenty-two of these patients had decreased LVEF relative to baseline at last evaluation, suggesting some decrement in function.

In addition to the five evaluable arm 1 patients with confirmed CEs, eight evaluable arm 1 patients reported symptoms of CD before recurrence that did not meet protocol criteria for a CE. Six patients have been followed for ≥ 6 months since onset of symptoms; all patients were asymptomatic and receiving no cardiac medications (Table 2).

Discontinuation of Trastuzumab Therapy in Patients in Arm 2

Trastuzumab treatment information was submitted quarterly. At least one treatment form has been submitted on 825 of 850 evaluable arm 2 patients, and 714 have completed trastuzumab, and all required documentation has been submitted. Trastuzumba was permanently discontinued before completion of 1 year of therapy or recurrence in 197 patients (28%) (Table 3). Trastuzumab was discontinued for cardiac-related reasons (asymptomatic decline in LVEF, symptoms of CD, or other cardiac symptoms) in 133 patients

Table 2. Follow-Up and Recovery of Evaluable Patients Reporting Symptoms of CD Suggestive of CHF

Treatment Arm	No. of Patients	
	AC → PTX	AC → PTX + H
Cardiac deaths	1	0
Patients with confirmed CHF	4	31
Followed ≥ 6 months from diagnosis of CHF	1	27
Reported symptoms during last 6-month F/U interval	1/1	1/27
On medications during last 6-month F/U interval	1/1	18/27
Patients reporting CD not meeting criteria for CHF	8	43
Followed ≥ 6 months from report of CD	6	39
Reported symptoms during last 6-month F/U interval	0/6	1/39
On medications during last 6-month F/U interval	0/6	8/39

Abbreviations: CD, cardiac dysfunction; CHF, congestive heart failure; AC, doxorubicin and cyclophosphamide; PTX, paclitaxel; H, trastuzumab; F/U, follow-up.

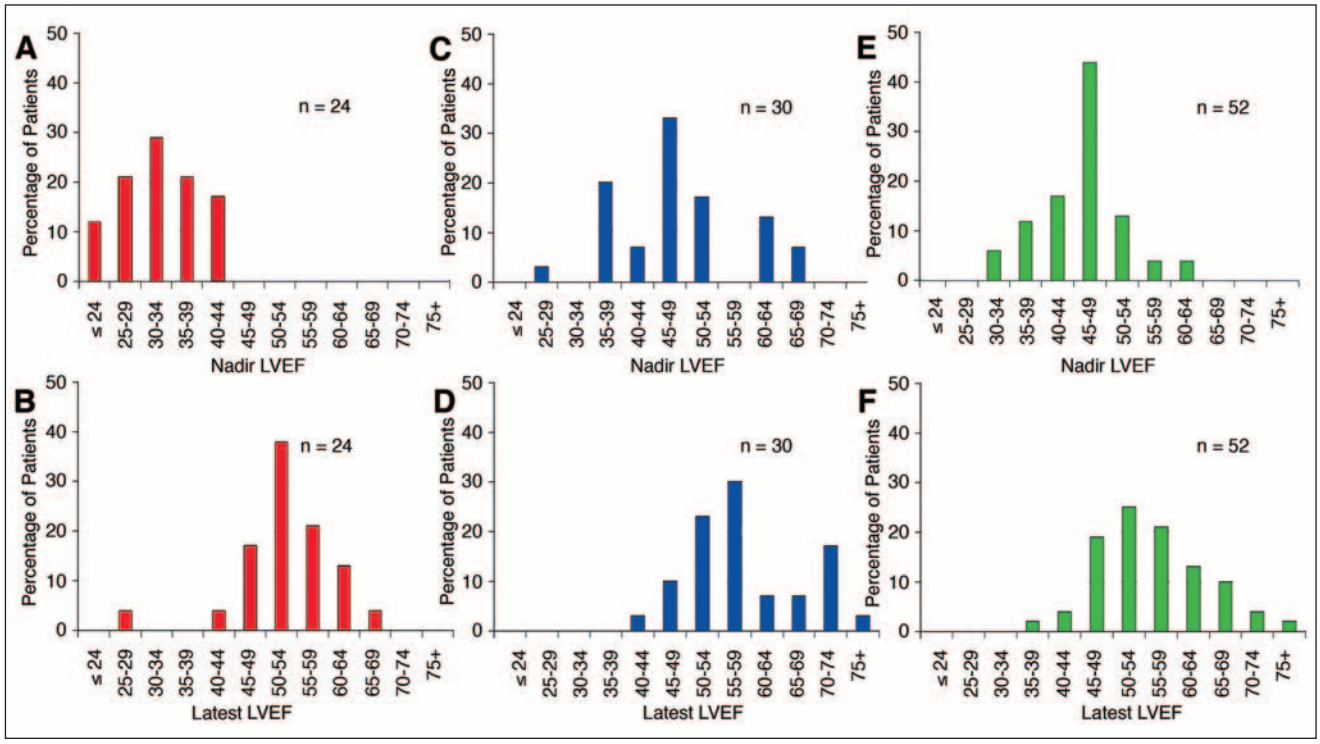


Fig 3. Histograms of left ventricular ejection fraction (LVEF) for the following three cohorts of evaluable patients in arm 2: (A, B) criteria met for congestive heart failure (CHF), (A) nadir LVEF and (B) latest LVEF; (C, D) symptoms of possible cardiac dysfunction but criteria not met for CE, (C) nadir LVEF and (D) latest LVEF; and (E, F) trastuzumab discontinued for asymptomatic decreases in LVEF, (E) nadir LVEF and (F) latest LVEF.

(19%), including 17 (2%) of 825 patients during the first quarter of therapy, 57 (8%) of 757 patients during the second quarter, 44 (7%) of 643 patients during the third quarter, and 15 (3%) of 538 patients during the final quarter.

Of 102 evaluable patients who discontinued trastuzumab because of asymptomatic declines in LVEF, 21 subsequently reported symptoms of possible CD and have been included in the previous cohorts. Of the remainder, LVEF has been reported in 52 patients ≥ 6 months after discontinuation. Their nadir and most recent LVEF results are shown in Figures 3E and 3F, where they are contrasted with the nadir and most recent results for trastuzumab-treated patients with confirmed CEs (Figs 3A and 3B) and patients who had symptoms of CD not meeting criteria for a CE (Figs 3C and 3D). Of these 52 patients, the most current LVEFs are less than 45% in three patients (6%) and less than 50% in 13 patients (25%).

Table 3. Reasons for Discontinuation of Trastuzumab Prior to 52 Weeks

Reason	No. of Patients	% of Evaluable Arm 2 Patients Who Have Completed Trastuzumab Therapy (n = 714)
Asymptomatic decrease in LVEF	102	14
Symptoms of CHF or other cardiac problems	31	4
Other toxicity/adverse event	14	2
Patient withdrawal	31	4
Other	19	3
Total	197	28

Abbreviations: LVEF, left ventricular ejection fraction; CHF, congestive heart failure.

Trastuzumab Treatment Holds Attributed to Symptomatic or Asymptomatic Cardiotoxicity

Trastuzumab was held for either asymptomatic declines in LVEF (Table 1) or possible cardiac symptoms. Thirty-one percent of evaluable patients temporarily held or permanently discontinued trastuzumab because of asymptomatic declines in LVEF (24%) and/or symptomatic cardiotoxicity (8%).

Cardiac Risk Factors and Incidence of CHF

Table 4 lists potential risk factors for CHF. LVEF, assessed either at baseline or after AC, was strongly associated with subsequent CHF ($P < .0001$), and age at entry was also predictive ($P = .03$). Hypertension was marginally significant ($P = .07$). In a multivariate analysis, age and post-AC LVEF remained statistically significant. There was no increase in CHF among women with left-sided lesions receiving radiotherapy (HR = 0.80; $P = .59$). Table 5 lists the

Table 4. Risk Factors for Trastuzumab/Chemotherapy Induced CHF

Risk Factor	No. of Patients	CHFs		P^*	Relative Risk	95% CI
		No.	%			
Race/ethnicity						
White	715	26	3.6	.10	Reference	
Black	60	2	3.3		0.90	0.21 to 3.8
Hispanic	27	0	0		0	—
Asian	25	3	12.0		3.7	1.1 to 12.1
Other/unknown	23	0	0		0	—
Age						
< 50 years	441	9	2.0	.03	Reference	
50-59 years	276	15	5.4		2.7	1.2 to 6.2
60+ years	133	7	5.3		2.7	1.0 to 7.3
History of smoking						
No	503	17	3.4	.46	1.3	0.65 to 2.7
Yes	321	14	4.4			
Left-sided tumor and radiation						
No	526	21	4.0	.59	0.80	0.38 to 1.7
Yes	313	10	3.2			
Family history of cardiac disease						
No	759	28	3.7	.73	1.3	0.40 to 4.3
Yes	61	3	4.9			
Any medications at baseline						
No	633	21	3.3	.28	1.6	0.77 to 3.4
Yes	192	10	5.2			
Hypertension medications						
No	664	21	3.2	.07	2.0	0.95 to 4.3
Yes	161	10	6.2			
Atrial fibrillation/arrhythmia medications						
No	825	31	3.8	NA	NA	
Yes	0	0	0	NA	NA	
Ventricular arrhythmia medications						
No	825	31	3.8	NA	NA	
Yes	0	0	0	NA	NA	
Diabetes medications						
No	797	31	3.9	.42	0	—
Yes	28	0	0			
Elevated fasting lipid profile medications						
No	759	30	4.0	.52	0.44	0.06 to 3.2
Yes	60	1	1.7			
Baseline LVEF						
50%-54%	62	9	14.5	.0001	Reference	
55%-64%	410	13	3.2		0.20	0.09 to 0.47
65%+	378	9	2.4		0.15	0.06 to 0.39
Post-AC LVEF						
50%-54%	96	12	12.5	< .0001	Reference	
55%-64%	425	16	3.8		0.28	0.13 to 0.60
65%+	320	3	0.9		0.07	0.02 to 0.25

Abbreviations: CHF, congestive heart failure; LVEF, left ventricular ejection fraction; NA, not applicable.
*Log-rank test for time to CHF.

3-year cumulative incidences of CHF among trastuzumab-treated patients as a function of post-AC LVEF and age. Results accorded with expectations for all patient groups except patients whose post-AC LVEF was marginally greater than LLN (ie, ≤ 54%). Among the 48 patients of age ≥ 50 years with LVEF in this range, nine experienced CHF, all within 7 months of initiating trastuzumab (cumulative incidence = 20%; 95% CI, 11% to 36%).

Changes in LVEF During Treatment

Patients accrued by June 30, 2003 have completed all MUGA scans through 18 months. In this group, the median baseline LVEF was 63%, and the median decrease after AC was 2% ($P < .0001$). The post-AC median decreases in the two arms were not statistically different ($P = .25$). In evaluable patients, there was an additional decrease in LVEF after paclitaxel with or without trastuzumab. Decrements were

Table 5. Three-Year Cumulative Incidence of CHF As a Function of Post-AC LVEF and Age in Evaluable B-31 Patients Receiving AC Followed by Paclitaxel Plus Trastuzumab

Age and Post-AC LVEF	No. of Patients	No. of CHFs	3-Year Cumulative Incidence (%)	95% CI (%)
≤ 49 years				
50%-54%	48	3	6.8	2.3 to 20.5
55%-64%	229	5	2.5	1.0 to 5.9
65%+	160	1	1.1	0.2 to 8.0
≥ 50 years				
50%-54%	48	9	20.0	11.1 to 35.9
55%-64%	196	11	6.1	3.4 to 10.9
65%+	160	2	1.5	0.4 to 6.1
All patients	841	31	4.1	2.9 to 5.8

Abbreviations: CHF, congestive heart failure; LVEF, left ventricular ejection fraction; AC, doxorubicin and cyclophosphamide.

greater in arm 2 than arm 1. At 6, 9, and 18 months, the median declines in LVEF from baseline values were 5%, 6%, and 4% in arm 2 compared with 3%, 2%, and 3% in arm 1. At each point, the decline was statistically significant compared with baseline ($P < .0001$). The decline in arm 2 after the initiation of trastuzumab was greater than in arm 1 (at 6 and 9 months, $P < .0001$; at 18 months, $P = .01$).

CREC Criteria

We computed the cumulative incidence of MUGA results meeting CREC criteria for asymptomatic CD (decline in LVEF ≥ 10 percentage points to < 55%) at least once during the 52 weeks beginning with day 1 of cycle 5. In the evaluable cohort, the incidence was 17% (95% CI, 15% to 20%) in arm 1 and 34% (95% CI, 31% to 38%) in arm 2 (HR = 2.1; 95% CI, 1.7 to 2.6; $P < .0001$).

DISCUSSION

It is reasonable to compare the 4.1% incidence of CHF in arm 2 with the 2.2% incidence of class III or IV CHF in metastatic patients treated with paclitaxel and trastuzumab in the CREC analysis.[3] However, comparison of incidence of CD that did not meet CHF criteria is difficult. Although 34% of B-31 arm 2 patients met CREC criteria for asymptomatic CD at least once during the 52 weeks after initiation of trastuzumab, the same was true for 17% of control patients. This rate of subclinical CD on the control arm was higher than the 13.2% rate of paclitaxel-trastuzumab–treated patients with metastatic cancer in the pivotal trial with any degree of CD.[3] The requirement for scheduled serial MUGA scans and the prospective reporting requirements in B-31 complicate comparison of rates of overall CD.

To more clearly quantify rates of overall CD, it may be more appropriate to consider only asymptomatic declines in LVEF that were persistent and thus required discontinuation of trastuzumab. Of the 714 arm 2 patients for whom complete treatment data are available, 135 (19%) discontinued trastuzumab because of asymptomatic or symptomatic CD (n = 133, including 29 patients with CD meeting criteria for class III or IV CHF) or completed 1 year of treatment but subsequently presented with CHF (n = 2). This percentage (19%) may be a reasonable summary of arm 2 patients experiencing some degree of CD, including but not limited to patients who experienced class III or IV CHF.

Whether a 4.1% incidence of class III or IV CHF and an overall CD incidence of 19% are acceptable in the adjuvant setting depends on the magnitude of benefit from the therapy. Based on the results of the joint analysis of B-31 and NCCTG N9831, this benefit is considerable. At 4 years, the estimated absolute improvement in disease-free survival is 18% (85% minus 67%; 95% CI, 13% to 24%), and, for overall survival, the benefit is 4.8% (91.4% minus 86.6%; 95% CI, 0.6% to 9.0%).[4] Another important consideration is reversibility of CD. The CHF associated with trastuzumab seemed to be responsive to cessation of therapy and management (Table 2), and LVEF generally recovered to nearly normal levels over time (Figs 3A and 3B). These findings suggest that CD associated with trastuzumab is qualitatively different than anthracycline cardiotoxicity.[8] However, at present, patients with CHF associated with trastuzumab therapy have been followed for, at most, several years, and longer follow-up is required to understand the impact of this toxicity on survival and quality of life. Similarly, patients experiencing milder symptomatic or asymptomatic CD also need to be followed to fully determine the long-term implications.

To address risk-benefit trade-offs, it is essential to evaluate potential predictive factors for increased risk of toxicity. Post-AC LVEF and age were associated with trastuzumab-associated CHF. Age was a significant predictor of cardiac risk in the CREC analysis[3] and is also a risk factor for doxorubicin-induced CD.[9]

Trastuzumab has been evaluated in the adjuvant setting using less cardiotoxic regimens than those in B-31. Recent data from NCCTG N9831 indicated delaying administration of trastuzumab until completion of paclitaxel may result in lower rates of severe CD.[10] However, an unplanned interim efficacy analysis of the N9831 data suggested that this approach may be less effective than concurrent administration.[10] Conversely, the Herceptin Adjuvant (HERA) trial, which compared trastuzumab to observation after completion of chemotherapy, resulted in little symptomatic CD and demonstrated improvement in disease-free survival comparable to the disease-free survival seen in B-31/N9831.[11] Currently, Breast Cancer International Research Group Study 006 is evaluating trastuzumab administered concurrently with docetaxel and carboplatin. Toxicity data from this trial indicate minimal CD.[12] If efficacy results are ultimately favorable, this study could support removal of anthracyclines from the chemotherapy regimen with which trastuzumab will be administered.

Given the marked reduction in recurrence and mortality afforded by the administration of trastuzumab with paclitaxel after AC, an assessment of risks and benefits indicates that the regimen is appropriate for most women with HER2-positive node-positive disease and adequate cardiac function. The regimen may not be appropriate for older patients whose post-AC LVEF is only marginally greater than LLN.

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Authors' Disclosures of Potential Conflicts of Interest

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