

## Dose-Dense Adjuvant Doxorubicin and Cyclophosphamide Is Not Associated With Frequent Short-Term Changes in Left Ventricular Ejection Fraction

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### A B S T R A C T

#### Purpose

Doxorubicin and cyclophosphamide (AC) every 3 weeks has been associated with frequent asymptomatic declines in left ventricular ejection fraction (LVEF). Dose-dense (dd) AC followed by paclitaxel (P) is superior to the same regimen given every third week. Herein, we report the early cardiac safety of three sequential studies of ddAC alone or with bevacizumab (B).

#### Patients and Methods

Patients with *HER2*-positive breast cancer were treated on two trials: ddAC followed by P and trastuzumab (T) and ddAC followed by PT and lapatinib. Patients with *HER2*-normal breast cancer were treated with B and ddAC followed by B and nanoparticle albumin-bound P. Prospective LVEF measurement by multigated radionuclide angiography scan before and after every 2 week AC for 4 cycles and at month 6 from all three trials were aggregated to determine the early risks of cardiac dysfunction.

#### Results

From January 2005 to May 2008, 245 patients were enrolled. The median age was 47 years (range, 27 to 75 years). Median LVEF pre-ddAC was 68% (range, 52% to 82%). LVEF post-ddAC was available in 241 patients (98%) and the median was unchanged at 68% (range, 47% to 81%). Per protocol no patients were ineligible for subsequent targeted biologic therapy based on LVEF decline post-ddAC. In addition, LVEF was available in 222 patients (92%) at 6 months, at which time the median LVEF was similar at 65% (range, 24% to 80%). Within 6 months of initiating chemotherapy, three patients (1.2%; 95% CI, 0.25% to 3.54%) developed CHF, all of whom received T.

#### Conclusion

Dose-dense AC with or without concurrent bevacizumab is not associated with frequent acute or short-term declines in LVEF.

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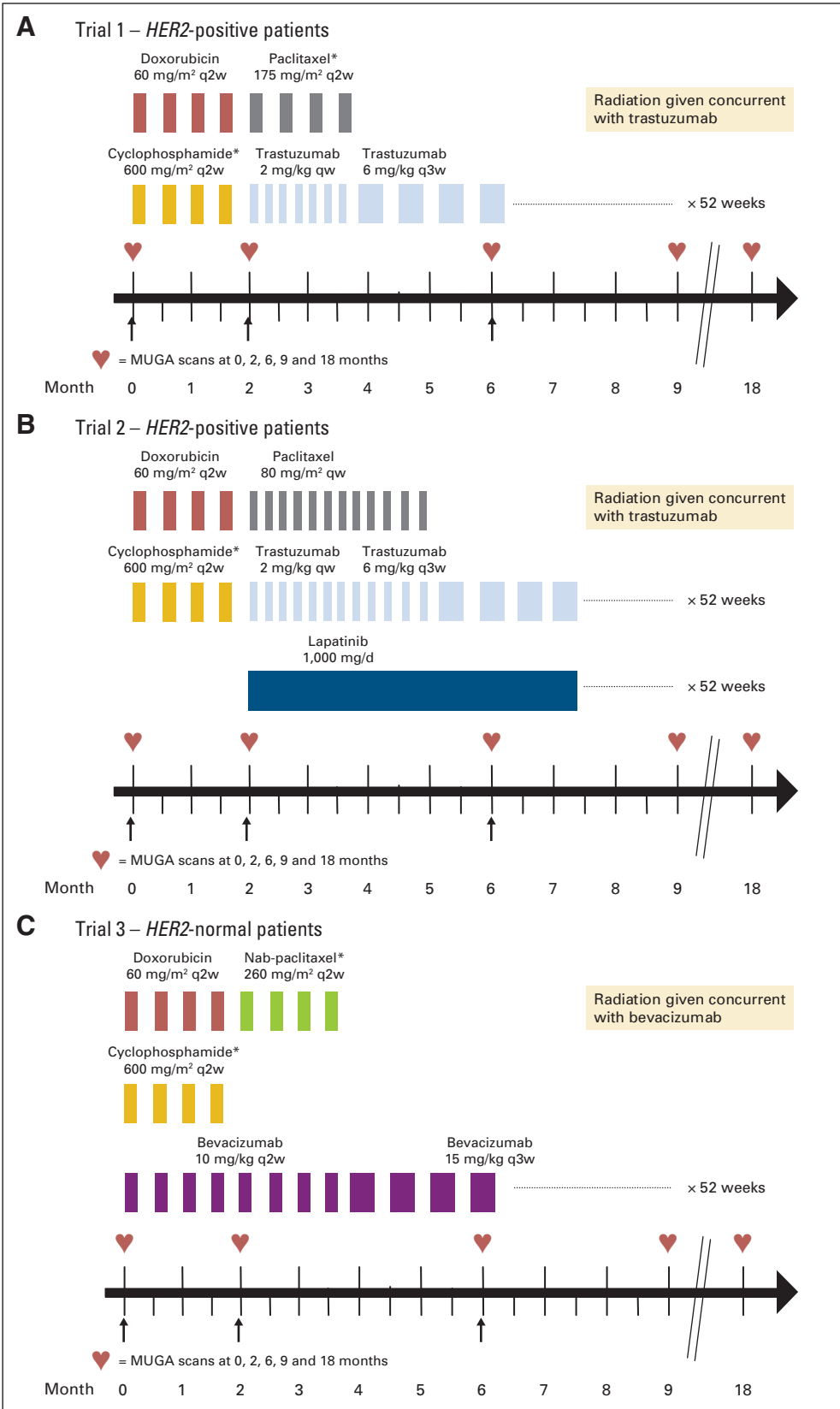
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### INTRODUCTION

The 2000 Early Breast Cancer Trialists Collaborative Group overview of polychemotherapy in breast cancer demonstrated that anthracycline-based regimens are superior to nonanthracycline-based therapies in terms of disease-free survival (DFS) and overall survival (OS).<sup>1,2</sup> However, the risk of long-term cardiomyopathy and congestive heart failure (CHF), related to total anthracycline dose, remains an important clinical concern.<sup>3</sup> In trials that have evaluated conventionally scheduled administration of doxorubicin and cyclophosphamide (AC) every 3 weeks for 4 cycles followed by a

taxane (several schedules), the incidence of CHF and changes in left ventricular ejection fraction (LVEF) ranged up to 2.5%.<sup>4-6</sup> Dose-dense (dd) chemotherapy with AC followed by paclitaxel (P) every other week improves DFS and OS when compared with conventionally scheduled AC every 3 weeks followed by P and had one half of the rate of grade 3 to 4 cardiac events.<sup>6-7</sup>

Cardiac toxicities were a concern when trastuzumab (T; Herceptin, Genentech, San Francisco, CA) was studied with conventionally scheduled chemotherapy in the adjuvant setting for patients with *HER2*-positive breast cancer.<sup>8-12</sup> Thus, rigorous cardiac follow-up was required, which included



**Fig 1.** (A-C) Schemas of all three trials. Black arrows indicate timing of LVEF (left ventricular ejection fraction) measurement reported in this analysis. q2w, every 2 weeks; qw, weekly; q3w, every 3 weeks; MUGA, multigated radionuclide angiography. (\*) Pegfilgrastim was given subcutaneously on day 2 after chemotherapy.

LVEF monitoring after the completion of AC every 3 weeks for 4 cycles in National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, North Central Cancer Treatment Group N9831, and Breast Cancer International Research Group (BCIRG) 006. In the combined analysis of NSABP B-31 and N9831, there was a patient drop-out rate of 6.7% due to significant asymptomatic LVEF declines after AC every 3 weeks that, per protocol prohibited these patients from progressing to the taxane and T phase.<sup>8</sup> In distinction to this experience, we showed that ddAC followed by P with T<sup>13</sup> did not lead to patient drop-outs after ddAC and in our pilot trial, all enrolled patients were able to proceed to receive P with T. Furthermore, the overall CHF rate was 1.4% (one of 70 patients)<sup>13</sup> as compared with the 2% to 4% rate reported with prior anthracycline and taxane regimens when given in an every 3 weeks schedule.<sup>8,11</sup> Based on these results, we conducted a second trial which differed only in the substitution of a weekly schedule for paclitaxel administration and the addition of lapatinib (ddAC followed by weekly P with T and lapatinib).<sup>14</sup>

For patients with *HER2*-normal breast cancer, bevacizumab (B) (Avastin, Genentech, San Francisco, CA), a humanized monoclonal antibody to vascular endothelial growth factor (VEGF) with proven efficacy in combination with chemotherapy for metastatic breast cancer,<sup>15</sup> is being tested in the adjuvant setting. In preparation, B was evaluated with ddAC followed by P in the Eastern Cooperative Oncology Group (ECOG) study 2104 and the incidence of symptomatic CHF with ddAC followed by P with B was 2%.<sup>16</sup> We conducted a similar feasibility trial combining B with ddAC followed by nanoparticle albumin-bound (nab) paclitaxel.<sup>17</sup> Because all three of our prospective studies delivered 4 cycles of every other week (dose-dense) AC (alone or with bevacizumab) with serial cardiac monitoring, we aggregated the baseline, post-AC (month 2) and month 6 ejection fraction assessments to address the short-term cardiac safety of ddAC for 4 cycles.

## PATIENTS AND METHODS

Patients with *HER2*-positive breast cancer as 3+ by immunohistochemistry or amplified by fluorescent in situ hybridization, regardless of nodal status or tumor size, were eligible for trial 1 (adjuvant/neoadjuvant ddAC followed by PT) at Memorial Sloan-Kettering Cancer Center (MSKCC). Subsequently, similar patients were eligible for trial 2 (ddAC followed by weekly PT plus lapatinib) conducted jointly by MSKCC, Dana-Farber/Harvard Cancer Center (including Dana-Farber Cancer Institute, Massachusetts General Hospital, and Beth Israel Deaconess Medical Center). Patients with *HER2*-normal breast cancer (node positive or high risk node negative) were eligible for trial 3, a B-based adjuvant study at MSKCC and University of California, San Francisco

(B and ddAC followed by B and nab-P). All patients had an absolute neutrophil count (ANC)  $\geq 1,000/\mu\text{L}$ , platelet count  $\geq 100,000/\mu\text{L}$ , normal total bilirubin and transaminases  $\leq 2.5$  upper limit of normal.

The LVEF by multigated radionuclide angiography (MUGA) scan had to be at or above 55% for trial 1 (ddAC followed by PT).<sup>13</sup> The minimal enrollment LVEF was subsequently lowered to  $\geq 50\%$  for trial 2 (ddAC followed by weekly PT plus lapatinib)<sup>14</sup> and trial 3 the B-containing study (B and ddAC followed by B and nab-P).<sup>17</sup> Patients who received B were also required to have a normal serum creatinine or a creatinine clearance  $\geq 60$  mL/min by the Cockcroft-Gault formula. Patients with a known history of unstable angina, myocardial infarction within 12 months, CHF, serious medical illnesses, inability to give consent, or who were pregnant were excluded. Patients with clinically significant peripheral vascular disease, a stroke within 12 months, or blood pressure higher than 150/100 mmHg were excluded from receiving B. Otherwise, patients were not excluded on the basis of controlled hypertension. All patients gave informed consent and all studies were reviewed and approved by the individual institutional review boards of each institution.

## Treatment

In all three studies AC (doxorubicin 60 mg/m<sup>2</sup> and cyclophosphamide 600 mg/m<sup>2</sup>) was given intravenously (IV) once every 14 days and supported by pegfilgrastim. In trial 1, this was followed by P (175 mg/m<sup>2</sup>) IV every 2 weeks for 4 cycles, with pegfilgrastim at 6 mg subcutaneously (SQ) on day 2. T was given IV weekly (4 mg/kg loading dose followed by 2 mg/kg) starting with paclitaxel and was continued every 3 weeks (6 mg/kg) after the completion of chemotherapy, for 1 year's duration (Fig 1A). In trial 2, AC was instead followed by P IV weekly (80 mg/m<sup>2</sup>) for 12 doses. T was given in the same fashion as in the pilot study above, but lapatinib (1,000 mg orally daily) was added concurrently with PT, for 1 year's duration (Fig 1B). In trial 3 (patients with *HER2*-normal breast cancer), AC was given concurrently with B (10 mg/kg) once every 2 weeks. This was followed by nab-P (260 mg/m<sup>2</sup>) IV every 2 weeks for 4 cycles, again with pegfilgrastim (6 mg SQ on day 2). After chemotherapy was completed, B was changed to 15 mg/kg once every third week for 12 cycles to complete 1 year of treatment (Fig 1C). Standard chemotherapy premedications were used. Patients with estrogen receptor- or progesterone receptor-positive tumors received tamoxifen or aromatase inhibitors as appropriate, and radiation therapy was recommended per institutional guideline.

## Cardiac Monitoring: LVEF Assessment

All patients underwent assessment of LVEF by MUGA scans at study enrollment, at month 2 (on completion of ddAC regardless of B usage), and at months 6, 9, and 18 (similar to NSABP B31 and N9831). In the *HER2*-positive group, T was held if the post-ddAC LVEF (month 2) declined by more than 15% or  $\leq 15\%$  to less than the lower limit of normal. In the *HER2*-normal group, since B was initiated with ddAC, adjustments of B were recommended based on the LVEF results. Three categories of asymptomatic LVEF decline were defined across the B-based study to guide physicians on whether to hold or continue it based on absolute asymptomatic declines in LVEF and the absolute value of LVEF as presented in Table 1. These categories were absolute decreases of less than 10%, 10 to 15%, and  $\geq 16\%$  (Table 1).

**Table 1.** Guidelines for Continuation or Discontinuation of Bevacizumab Based on LVEF Results for ddAC Plus Bevacizumab Followed by Nanoparticle Albumin-Bound Paclitaxel Plus Bevacizumab

LVEF on MUGA	Absolute Decrease		
	< 10%	10% to 15%	$\geq 16\%$
$\geq 55\%$	Continue bevacizumab	Continue bevacizumab	Hold bevacizumab and repeat MUGA after 4 weeks
50%-54%	Continue bevacizumab and repeat MUGA in 4 weeks	Hold bevacizumab and repeat MUGA after 4 weeks	Hold bevacizumab and repeat MUGA after 4 weeks
$\leq 49\%$	Hold bevacizumab and repeat MUGA after 4 weeks	Hold bevacizumab and repeat MUGA after 4 weeks	Hold bevacizumab and repeat MUGA after 4 weeks

Abbreviations: LVEF, left ventricular ejection fraction; ddAC, dose-dense doxorubicin and cyclophosphamide; MUGA, multigated radionuclide angiography.

**Table 2.** Baseline Ages of Patients

	AC-PT		AC, PT, and Lapatinib		AC + B		Overall	
	No.	%	No.	%	No.	%	No.	%
No. of patients	70		95		80		245	
Median age, years	49		46		48		47	
Range	27-72		28-73		27-75		27-75	
< 40	14	20	20	21	15	19	49	20
40-49	23	33	37	39	30	38	90	37
50-59	22	31	29	31	24	30	75	31
60-69	9	13	8	8	10	12	27	11
70+	2	3	1	1	1	1	4	1
Surgery								
Lumpectomy	36	51	36	38	23	29	94	38
Modified radical mastectomy	34	49	59	62	57†	71	151	62
Pre-existing hypertension	11	16	17	18	10	13	37	15
Radiation								
Breast/chest	50	71	74	78	56	70	172	69
Left sided	21	42	38*	51	23/56	41	81/172	47
Right sided	29	58	37*	50	33/56	59	91/172	53

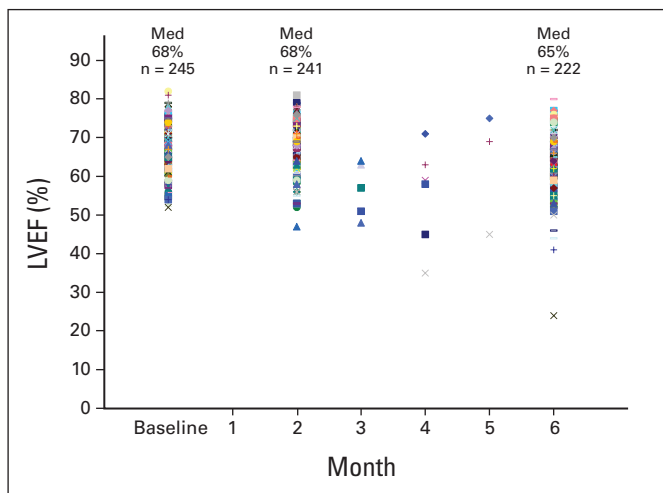
Abbreviations: AC, doxorubicin and cyclophosphamide; PT, paclitaxel and trastuzumab; B, bevacizumab.  
 \*Includes one patient who received bilateral radiotherapy.  
 †Includes one patients with prior mastectomy and subsequent ipsilateral recurrence.

**RESULTS**

From January 2005 to May 2008, 245 patients were enrolled in the three trials. The median age was 47 years (range, 27 to 75 years; Table 2). There were 165 patients on the T-containing studies (70 in trial 1 and 95 in trial 2) and 80 patients on the B-containing study. Overall, 231 patients (94%) received chemotherapy in the adjuvant setting and 14 (6%) were treated in the neoadjuvant setting. The median baseline LVEF was 68% (range, 52% to 82%; Fig 2). This was similar for the groups treated with bevacizumab (median, 68%; range, 53% to 82%) or not (median, 68%; range, 52% to 81%).

**Cardiac Safety After ddAC Alone or With B**

*At month 2.* Results on LVEFs were available in 241 of 245 patients (98%) at month 2 (one withdrew consent and declined both



**Fig 2.** Absolute LVEF (left ventricular ejection fraction) values over time. Med, median.

treatment and MUGA scans, one discontinued treatment and was lost to follow-up, one developed progressive breast cancer, and one developed viral pneumonia and multisystem organ failure with sepsis and died after AC cycle 2; on review CHF did not contribute to her death).

The post-ddAC LVEF at month 2 was normal in 240 of 241 patients (99%; 95% CI, 97.7% to 99.9%). The LVEF was similar whether patients received B (median, 68%; range, 53% to 80%) or not (median, 68%; range, 47% to 81%). In both the *HER2*-positive and *HER2*-normal groups (after ddAC and B-ddAC, respectively), no patients stopped treatment at month 2 because of a significant asymptomatic LVEF decline. Only one patient in the entire three-study cohort had an asymptomatic LVEF decline to below the lower limit of normal immediately after ddAC for 4 cycles (Fig 2). After ddAC, this patient (in trial 2) had an LVEF decline from 68% to 47% on a MUGA scan at an outside institution. Per protocol, this patient did not begin anti-*HER2* therapy immediately. A MUGA at MSKCC 1 month later revealed normal LVEF (64%) and anti-*HER2* therapy was initiated per protocol, with no further LVEF declines to date. One other patient (in trial 3) had an asymptomatic LVEF decline exceeding 15% after B and ddAC (71% to 53%). After the interruption in B, this improved to 64% 4 weeks later and B was reintroduced; per protocol, this patient remained on study.

An asymptomatic LVEF decline of more than 15% after ddAC occurred in only two patients of 241 evaluable (0.8%; 95% CI, 0.1% to 3.0%). One of these patients received B and ddAC and the other ddAC alone as detailed above. An asymptomatic LVEF decline of 10% to 15% occurred in seven (3%; 95% CI, 1.1% to 5.9%) of 241 patients (three had ddAC and four had B and ddAC); five of these patients had subsequent improvement in LVEFs and continued treatment, one withdrew consent and one developed progressive breast cancer. Of the 241 patients, 96 (40%, 95% CI, 33.6% to 46.3%) had LVEF declines of less than 10%. The majority of patients, 136 of 241 (56%; 95% CI, 49.9% to 62.8%) had stable or improved LVEFs compared to baseline values (Table 3).

**Table 3.** Change in LVEF After Dose-Dense AC With or Without Bevacizumab (months 2 and 6)

Change in LVEF	Month 2		Month 6	
	No. of Patients	%	No. of Patients	%
Total patients	241		222	
Decrease				
≥ 16%	2	0.8	7*	3
10%-15%	7	3	24	11
< 10%	96	40	102	46
5-< 10%	35	15	46	21
< 5%	61	25	56	25
Stable or improved	136	56	89	40

Abbreviations: LVEF, left ventricular ejection fraction; AC, doxorubicin and cyclophosphamide.  
\*This includes one patient with congestive heart failure and LVEF decline ≥ 16% who had month 6 LVEF measured per protocol.

At month 6. Results were available in 222 of 241 patients (92%) at 6 months (one expired from hepatitis B reactivation, five withdrew consent, 11 had toxicities [noncardiac] and two had CHF and did not have month 6 LVEF assessments). At month 6, the LVEF was normal in 217 of 222 patients (98%; 95% CI, 94.8% to 99.3%) and the median LVEF was 65% (range, 24% to 80%; Fig 2). This was similar whether patients received bevacizumab (median, 64%; range, 51% to 77%) or not (median, 65%; range, 24% to 80%). Three patients had an asymptomatic LVEF decline to below the normal limit. An asymptomatic decline of more than 15% occurred in six of 222 evaluable patients (3%; 95% CI, 1% to 5.8%) and all six had subsequent improvement in LVEF; a symptomatic decline of more than 15% occurred in one of 222 evaluable patients (0.5%, 95% CI, 0.01% to 2.5%) who developed CHF at 6 months of evaluation. An asymptomatic LVEF decline of 10% to 15% occurred in 24 of 222 patients (11%; 95% CI, 7.1% to 15.7%). LVEF declines of less than 10% were common and occurred in 102 of 222 patients (46%; 95% CI, 39.3% to 52.7%). The LVEF was stable or improved in 89 of 222 patients (40%; 95% CI, 33.6% to 46.9%; Table 3).

Within 6 months of initiating chemotherapy, a total of three of 245 patients (1.2%; 95% CI, 0.25% to 3.54%) had developed CHF, all of whom received anti-HER2 therapy (one in trial 1 and two in trial 2; Table 4). One additional patient treated on trial 2 developed CHF at

month 12. Therefore, at 1 year, the respective CHF rates for trials 1, 2, and 3 were 1.4%, 3%, and 0% (median follow-up of 28, 12, and 18 months).<sup>13,14</sup> In addition, one (1.3%, 95% CI, 0.03% to 6.8%) of 80 patients in trial 3 developed CHF at month 15 (3 months after completing therapy).<sup>17</sup>

## DISCUSSION

To our knowledge, this is the first report of the acute cardiac safety of ddAC with or without B measured prospectively. We did not confirm the previously reported high rate (6.7%) of significant asymptomatic declines in LVEF with conventionally scheduled AC.<sup>8</sup> In both trials for the HER2-positive patients, only one patient (in trial 2) had a treatment delay after ddAC due to an asymptomatic LVEF decline. Repeat MUGA at the parent institution was normal and allowed this patient to commence anti-HER2 therapy. Unlike trial 1 where all patients were required to have serial MUGA scans performed at only one institution, patients in trial 2 were permitted to have MUGAs done at various local facilities and it was possible that this might have added variability in the LVEF results. In the HER2-normal group where ddAC was given with concurrent bevacizumab, only one (1.2%) of 80 patients had a significant (> 15%) asymptomatic (and temporary) LVEF decline after ddAC. In this study, four (5%) of 78 evaluable patients receiving concurrent B and ddAC had asymptomatic absolute LVEF declines of more than 10% from baseline after 4 cycles of B and ddAC. This compared favorably to ECOG 2104 in which 13 (14%) of 93 patients receiving concurrent B and ddAC had asymptomatic LVEF declines more than 10%. In comparison to ECOG 2104 in which CHF occurred in 2% of patients receiving concurrent B and ddAC with a median follow-up of 14.6 months, the CHF rate in our B-based study was 1.3% with a median follow-up of 18 months.<sup>17</sup>

Of note, there were other studies that have evaluated the combination of B with an anthracycline. One example was a study by Wedam et al<sup>18</sup> on the combination of B with doxorubicin and docetaxel (50 mg/m<sup>2</sup> and 75 mg/m<sup>2</sup>) for 6 cycles every 3 weeks in the preoperative setting. In this study of 21 patients, no patient had a decline in LVEF of greater than 15%. Thus, an anthracycline combined with B appeared to be feasible in these studies which was consistent with our trial 3, in which B was combined with ddAC.

**Table 4.** Patients With CHF

Patient No.	Age (years)	Treatment	LVEF			
			At Baseline	At Month 2	At CHF Diagnosis	At Follow-Up
1*	56	ddAC → P-trastuzumab	> 75%	79%	CHF at month 4 ↓ 45% (ECHO)	50% 5 months and 58% 22 months later
2†	44	ddAC → weekly P- trastuzumab-lapatinib	68%	68%	CHF at month 3 ↓ 48% (ECHO)	62% (ECHO) 6 months later
3‡	35	ddAC → weekly P- trastuzumab-lapatinib	52%	56%	CHF at month 6 ↓ 24% (ECHO)	24% 2 months later

Abbreviations: CHF, congestive heart failure; LVEF, left ventricular ejection fraction; ECHO, echocardiogram; ddAC, dose-dense doxorubicin and cyclophosphamide; P, paclitaxel.

\*Patient 1 developed shortness of breath with clinical CHF at month 4. She was treated with a diuretic, a beta blocker, and an angiotensin-converting enzyme (ACE) inhibitor. Trastuzumab was discontinued per protocol. Her LVEF subsequently improved and she is currently clinically well.

†Patient 2 developed pleuritic chest pain and acute respiratory distress at month 3 and was diagnosed with CHF. She was stabilized on a diuretic and an ACE inhibitor. Per-protocol P-trastuzumab-lapatinib was discontinued. Six months after this event, she is clinically stable and off all cardiac medications.

‡Patient 3 had exertional dyspnea at month 6 and was found to have an LVEF of 24%. She came off P-trastuzumab-lapatinib and was treated with a beta blocker, digoxin, and a diuretic with improvement in symptoms. Four months after this event she has completed right-sided chest radiotherapy and is considering a permanent pacemaker.



The LVEF monitoring in our three studies was similar to that in NSABP B-31 and N 9831.<sup>8</sup> Across all three of our studies asymptomatic declines in LVEF were more common at month 6 compared to month 2. This likely reflected the predicted, additional effect of anti-HER2 therapy on LVEF. The majority of these declines occurred in patients treated with T with or without lapatinib, again suggesting that HER2-targeting agents contributed to these asymptomatic declines, likely due to the interaction with the prior anthracycline. Notably, the patients in our studies who developed CHF during treatment all received anti-HER2 therapies. Similarly, in the B-31 study, 28 of 31 patients developed CHF during the year of T (like our patients).<sup>19</sup> In addition in N9831 the cumulative 1-, 2-, and 3-year CHF rates were unchanged at 3.3%.<sup>20</sup> Thus, we now have long-term data out to at least a year and do not expect these rates to increase with longer follow-up. We see no early signal of higher rates of CHF when incorporating HER2-targeting agents into ddAC compared with every 3-weekly AC.

The apparent relative short-term cardiac safety of dose-dense AC in our three consecutive studies may not be expected by many in the medical oncology community. We believe that there are several possible explanations for our favorable outcomes. First, in terms of cardiotoxicity ddAC is at least as safe as every 3-weekly AC.<sup>6-7</sup> With a long-term follow-up of 6.5 years, the Cancer and Leukemia Group B study 9741 showed that in patients treated with ddAC followed by P, the grade 3 to 4 cardiac event rate was one half of that noted in those treated with the every 3-weekly schedule of the same chemotherapy.<sup>6-7</sup> Second, within the limited number of centers participating in these studies, there may have been greater standardization of the interpretation of MUGA scans based on the use of consistent equipment and readers. This is further supported by the two patients (both in trial 2), who had LVEF declines to below the lower limit of normal at outside institutions with normalization of LVEF at the main center. If this hypothesis is correct, the reproducibility of LVEF measurement by MUGA in different institutions is a potential problem in larger multicenter studies. Furthermore, there is some evidence that LVEF measurement with MUGA, as used in these trials, may be more reproducible than that with echocardiograms.<sup>21</sup> This, too, could have profound implications for the routine use and management of anthracyclines and T in much of the world. Albeit low, the LVEF changes that were noted in our three studies may be a concern later, and the changes that were not seen could be due to variable LVEF readings when dealing with multicenter trials. Third, the inherent subtle investigator bias in patient selection within our three studies may have excluded patients at a higher risk of cardiac dysfunction. In this case, the large multicenter trials may be more representative of a less selected patient population. However, we see no evidence of a differential protocol-enrollment selection bias in our trials as compared to the cooperative group trials. As an example, patients on the NSABP B-31 and N9831<sup>8</sup> trials had similar ages at baseline as our patients in trial 1 and the studies had similar cardiac exclusion criteria.<sup>13</sup>

Given the cardiotoxicity risks of anthracyclines, T, and possibly B, adjuvant trials involving these drugs have incorporated rigorous cardiac monitoring for asymptomatic declines in LVEF. This has led to the widespread recognition and concern about asymptomatic short-term declines in ejection fraction measured by MUGA and/or echocardiogram because these have been used as surrogates for the long-term risk of CHF.<sup>3</sup> The true significance is, however, unclear as many more patients have been noted to have these changes in the prospective randomized trials than those who actually ever develop

clinical CHF. With the large numbers of patients treated with anthracyclines, there are no clear available data to confirm a significant long-term impact of early asymptomatic LVEF change.

Our combined analysis of three trials adds new information on the risk of early asymptomatic ejection fraction change related to a more effective (dd) schedule of administration for AC. In patients receiving ddAC alone or with B, we did not identify a significant incidence of short-term cardiac toxicity. Longer-term follow-up of cardiac toxicity of ddAC with and without B, T, and lapatinib is ongoing. The assessment of biomarkers for cardiac injury in ongoing and future trials may allow us to see if there is any correlation with asymptomatic declines in LVEF.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

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