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Cardiac safety of adjuvant pegylated liposomal doxorubicin with concurrent trastuzumab: a randomized phase II trial

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Background: The cardiac safety of trastuzumab concurrent with pegylated liposomal doxorubicin (PLD) in an adjuvant breast cancer treatment regimen is unknown.

Patients and methods: Women with resected node-positive or intermediate-risk node-negative HER2 overexpressing breast cancer and baseline left ventricular ejection fraction (LVEF) ≥55% were randomized (1 : 2) to doxorubicin 60 mg/m^2 (A) + cyclophosphamide 600 mg/m^2 (C) every 21 days (q21d) for four cycles or PLD 35 mg/m^2 + C q21d + trastuzumab 2 mg/kg weekly (H) for 12 weeks. Both groups then received paclitaxel (Taxol, T) 80 mg/m^2 with H for 12 weeks followed by H to complete 1 year. The primary end point was cardiac event rate or inability to administer 1 year of trastuzumab.

Results: Of 181 randomized patients, 179 underwent cardiac analysis. The incidence of cardiac toxicity or inability to administer trastuzumab due to cardiotoxicity was 18.6% [$n = 11$; 95% confidence interval (CI) 9.7% to 30.9%] with A + C → T + H and 4.2% ($n = 5$; 95% CI 1.4% to 9.5%) with PLD + C + H → T + H ($P = 0.0036$). All events, except one, were asymptomatic systolic dysfunction or mildly symptomatic heart failure. Mean absolute LVEF reduction at cycle 8 was greater with doxorubicin (5.6% versus 2.1%; $P = 0.0014$).

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Conclusion: PLD + C + H → T + H is feasible and results in lower early cardiotoxicity rates compared with A + C → T + H.

Key words: adjuvant therapy, anthracyclines, breast cancer, cardiotoxicity, pegylated liposomal doxorubicin, trastuzumab

introduction

The concurrent or sequential administration of both anthracyclines and taxanes is commonly recommended for moderate- to high-risk breast cancer in the adjuvant setting. The incorporation of trastuzumab for HER2-positive disease improves disease-free and overall survival and has become a standard of care [1–4]. Retrospective analyses of several studies have observed that the benefit of adjuvant anthracycline-containing regimens may be limited to patients with HER2 overexpressing disease [5–9], although the final results from BCIRG 006, a large randomized phase III trial comparing adjuvant anthracycline- and non-anthracycline-containing trastuzumab-based regimens, is awaited [4].

Recent data suggest that the efficacy of adjuvant trastuzumab may be greater when given concurrently with taxanes rather than subsequent to anthracycline–taxane chemotherapy regimens [10]. A small phase III trial has demonstrated that concurrent administration of trastuzumab with neoadjuvant chemotherapy including paclitaxel and fluorouracil, epirubicin, and cyclophosphamide was associated with high pathological complete response rates and low cardiac toxicity [11, 12]. Currently, however, this strategy is generally limited to non-anthracycline regimens due to expectations of severe dose-limiting cardiotoxicities with concurrent conventional anthracyclines, especially doxorubicin, as observed in the pivotal trial for metastatic HER2 overexpressing disease [13].

Compared with conventional anthracyclines, pegylated liposomal doxorubicin (PLD) has been observed to be significantly less cardiotoxic in the metastatic setting [14–16]. A Canadian multicenter single-arm phase II trial evaluated the safety and efficacy of PLD 35 mg/m^2 combined with cyclophosphamide 600 mg/m^2 every 3 weeks as first-line treatment of metastatic breast cancer in 70 patients previously exposed to adjuvant anthracyclines and observed an objective response rate of 38%, median progression-free survival of 12.2 months, and a median survival time of 16.5 months [17]. The most common grade 3 toxicity was palmar-plantar erythrodysesthesia (PPE) occurring in seven patients (10%). Asymptomatic, reversible cardiac dysfunction [left ventricular ejection fraction (LVEF) drop of ≥10%] occurred in five patients (7.1%).

Five phase II studies have examined concurrent trastuzumab–PLD combinations for metastatic HER2 overexpressing breast cancer [18–22]. Among the total of 141 patients accrued, only 1 (0.7%) developed symptomatic congestive heart failure (CHF). Milder cardiotoxicity, consisting primarily of asymptomatic declines in LVEF, occurred in 5%–25%. Across all studies, the most commonly observed grade 3/4 toxic effects were PPE (13%–38%) and neutropenia (17%–27%) with PLD plus trastuzumab.

Based on these findings, we hypothesized that substituting PLD for doxorubicin may permit concurrent administration of trastuzumab with anthracyclines in the adjuvant setting and conducted this randomized phase II study evaluating the safety of an adjuvant concurrent trastuzumab–anthracycline regimen.

patients and methods

This study was a multinational, parallel group, randomized open-label trial. Subjects were randomized using a web-based randomization system in a 1 : 2 ratio (doxorubicin : PLD) and were stratified by age (<55 and ≥55 years).

patients

Eligible patients were women ≥18 years of age with operable node-positive or intermediate-risk node-negative [23], HER2 overexpressing histologically confirmed breast adenocarcinoma without evidence of metastatic disease. Eligible node-positive patients had T1-3, N1-2 stage tumors. Eligible node-negative patients had tumors >2 or >1 cm with at least one of the following features: negative estrogen receptor/progesterone receptor status, grade 2–3 histology, peritumoral lymphovascular invasion, or age <35 years. HER2 overexpression was locally determined by FISH or immunohistochemistry (3+). Patients had to have curative surgery including an axillary node dissection or negative sentinel node biopsy before randomization. Baseline LVEF ≥55% using multiple gated acquisition (MUGA) scan or echocardiogram (ECHO) was required as was an Eastern Cooperative Oncology Group performance status of zero to one and adequate bone marrow, renal, and liver function.

Exclusion criteria included prior radiotherapy, chemotherapy, or biotherapy for the currently diagnosed breast cancer; personal history of breast cancer; history of non-breast malignancy within 5 years of study entry except *in situ* carcinoma of the cervix or colon, melanoma *in situ*, or basal or squamous cell carcinoma of the skin; serious cardiac illness (including but not limited to history of, or active, CHF, history of or active treatment of any form of cardiomyopathy, history of or medication-requiring active angina pectoris, history of documented transmural myocardial infarction, serious ventricular arrhythmias requiring medication or implantable cardioverter–defibrillator therapy, uncontrolled supraventricular arrhythmias, clinically significant valvular disease, or poorly controlled hypertension [systolic blood pressure > 180 mmHg or diastolic blood pressure > 100 mmHg]); grade >2 neuropathy; chronic obstructive pulmonary disease requiring chronic treatment; clinically significant active infection; and unstable diabetes mellitus.

end points

The primary end point of this study was to determine separately in each arm the overall cardiac toxicity rate or the inability to administer trastuzumab due to cardiotoxicity, for the planned treatment duration of 1 year, consistent with current standards of care. Events included cardiac toxic effects, inability to administer trastuzumab during eight cycles of chemotherapy, or inability to administer trastuzumab for a duration of 1 year. Each patient could contribute only one event to the primary end point.

Cardiac toxic effects were categorized as level 1 (severe) or level 2 (mild). Level 1 cardiac toxic effects were defined as cardiac death due to heart failure, myocardial infarction or arrhythmia, or probable cardiac death (defined as sudden unexpected death within 24 h of a definite or probable

cardiac event) or severe symptomatic heart failure (New York Heart Association [NYHA] class III or IV), concomitant with a drop in LVEF by >10 percentage points from baseline and to <50% LVEF. Level 2 cardiac toxic effects were defined as asymptomatic systolic dysfunction (NYHA class I) or mildly symptomatic heart failure (NYHA class II) concomitant with a drop in LVEF of >10 percentage points from baseline and to < 50% LVEF.

Secondary end points included (i) incidence of overall, level 1 and 2 cardiac toxicity after four cycles of anthracycline-based chemotherapy, over the eight total cycles of chemotherapy (only one event contributed per patient), and during the 12 months following randomization, (ii) inability to administer trastuzumab due to cardiotoxicity during the four cycles of anthracycline-based chemotherapy, over the eight total cycles of chemotherapy, and during planned trastuzumab monotherapy.

The protocol was initially designed to evaluate relapse-free survival in the two treatment arms. Unfortunately, limitations in available resources precluded this analysis.

treatment

Eligible subjects were randomized to receive doxorubicin 60 mg/m^2 (A) i.v. plus cyclophosphamide 600 mg/m^2 (C) i.v. every 21 days for four cycles (arm A; A + C) or PLD 35 mg/m^2 i.v. plus cyclophosphamide 600 mg/m^2 i.v. given every 21 days plus trastuzumab (H) 2 mg/kg i.v. (first dose 4 mg/kg i.v.) given weekly for 12 weeks (arm B; PLD + C + H). Both groups then received paclitaxel 80 mg/m^2 (T) i.v. with trastuzumab 2 mg/kg i.v. (4 mg/kg i.v. for first dose if applicable) given weekly for 12 weeks (T + H), followed by trastuzumab monotherapy to complete 1 year. Premedications were used according to local institutional standards. Use of adjuvant endocrine and radiation therapy was at the investigators' discretion.

Primary prophylaxis with hematopoietic growth factors and antibiotics was not permitted; secondary prophylaxis was allowed per institutional standards. Dose reductions for grade 4 neutropenia lasting >7 days, febrile neutropenia, or grade 4 thrombocytopenia were, for the first episode, 75% reduction of doxorubicin and PLD and maintenance of paclitaxel and, for the second episode, 50% reduction of doxorubicin and 75% reduction of PLD and paclitaxel. Discontinuation of all three cytotoxic agents occurred with a third episode.

For the first four cycles of chemotherapy, trastuzumab was discontinued for level 1 or 2 cardiac toxicity or for LVEF <50%. For paclitaxel–trastuzumab and single-agent trastuzumab, the protocol recommended that trastuzumab be held for LVEF <50% concomitant with a drop of >10 points from baseline and resumed in 4 weeks if LVEF rose to ≥50% or drop reduced to ≤10 perentage points from baseline.

Dose and schedule modifications of PLD for PPE varied according to severity, duration, and occurrence of prior toxicity (see Table 1). Symptomatic management of PPE was at investigator discretion and no prophylactic therapies were permitted.

assessments

Cardiac assessments included a careful clinical evaluation for signs or symptoms of CHF and LVEF measurement with either MUGA or ECHO. The protocol recommended that one method be used consistently throughout the study. A drop in LVEF was to be reconfirmed within 3–4 weeks of occurrence. Clinical cardiac assessment occurred at baseline, before each cycle of therapy, post cycle 8, and at each follow-up visit. LVEF assessment occurred at baseline, before cycle 5, post cycle 8, and then per local institutional standards. After completion of chemotherapy, patients were followed every 3 months for 1 year and every 6 months for an additional year. For patients receiving post-study trastuzumab, the protocol recommended LVEF assessment according to the trastuzumab package insert, which includes repeat assessment every 3 months during treatment and at 6 months, 12 months, and 24 months following cessation of treatment [24]. Adverse events (AE) were graded according to the National Cancer Institute—Common Toxicity Criteria for AE version 3.0.

statistics

Based on an assumed cardiac risk ratio of < 2, the required sample size for 80% power to detect this difference was 1050. Limitations in available resources precluded accrual to this target; thus, no formal power calculations were conducted and the statistical plan was modified to determine event rates between the two treatment arms rather than allowing for powered statistical comparisons. The planned sample size was 180 patients (60 patients in the A + C → T + H arm and 120 patients in the PLD + C + H → T + H arm). Formal statistical sample size calculations were not used to determine sample size; 95% confidence intervals were calculated to provide the reference of estimation with 120 subjects for arm B. Having ∼60 subjects in arm A provided at least 10% precision for estimating the incidence of cardiac events in this arm. Demographic and baseline characteristics were summarized with descriptive statistics. Primary and secondary end points were analyzed on the intent-to-treat (ITT) population (all randomized subjects who received at least one dose of study treatment) and on the modified ITT population (the ITT population with two patients excluded for baseline LVEF <55%). The pooled incidences of level 1 and 2 cardiac events as well as the individual incidences were calculated with 95% confidence. The frequency of patients not being able to initiate or requiring hold or suspension of trastuzumab was calculated. An interim analysis occurred when half of the subjects on the PLD + C + H → T + H arm completed eight cycles and, at that time, the independent data and safety management committee permitted the trial to proceed to full accrual.

ethics

The study was conducted in accordance with ICH/GCP guidelines, approved by local institutional review boards, and monitored by an

Table 1. Pegylated liposomal doxorubicin (PLD) dose and schedule modification for palmar-plantar erythrodysesthesia (PPE)

Toxicity grade	Week after prior PLD dose		
	Week 3	Week 4	Week 5
1 without prior grade ≥3 PPE	Redose without modification	Redose without modification	Decrease dose by 25%
1 with prior grade ≥3 PPE	Hold 1 week	Hold 1 week	Decrease dose by 25%
2	Hold 1 week	Hold 1 week	Decrease dose by 25%
3	Hold 1 week	Hold 1 week	Study withdrawal
4	Hold 1 week	Hold 1 week	Study withdrawal

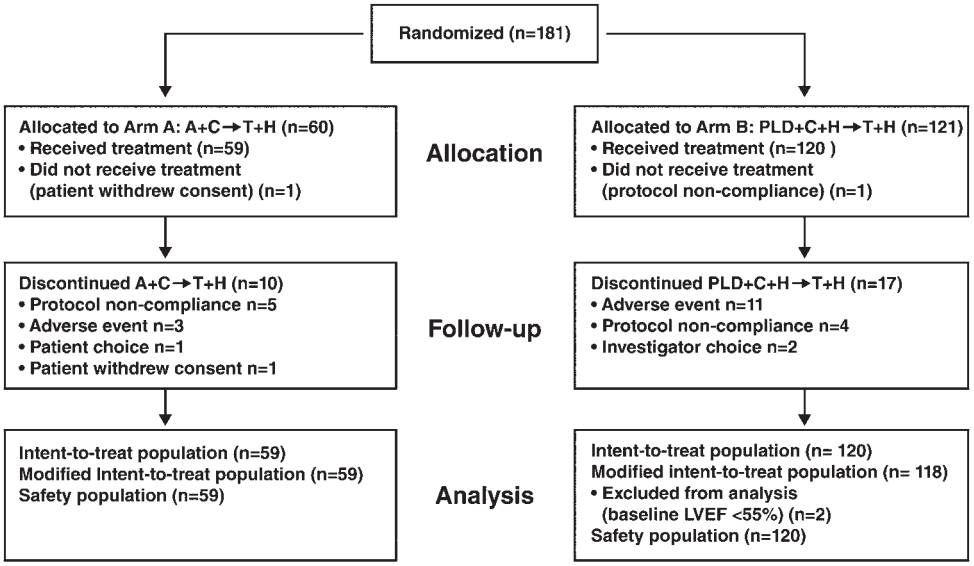

Figure 1. CONSORT diagram. A + C → T + H, doxorubicin plus cyclophosphamide followed by paclitaxel plus trastuzumab; PLD + C + H → T + H, pegylated liposomal doxorubicin plus cyclophosphamide plus trastuzumab followed by paclitaxel plus trastuzumab; LVEF, left ventricular ejection fraction.

Table 2. Baseline patient characteristics

	Arm A (A + C → T + H) (*N* = 59)	Arm B (PLD + C + H → T + H) (*N* = 120)
	No. (%)	No. (%)
Mean age, years (range)	52.5 (30–71)	50.2 (20–83)
Mean BSA, m^2 (range)	1.8 (1.39–2.38)	1.7 (1.42–2.39)
Race		
White	55 (93.2)	116 (96.7)
Black	3 (5.1)	1 (0.8)
Other	1 (1.7)	3 (2.5)
ECOG performance status		
0	52 (88.1)	115 (95.8)
1	6 (10.2)	5 (4.2)
Missing	1 (1.7)	0 (0)
ER status		
ER+	34 (57.6)	67 (55.8)
ER−	25 (42.4)	52 (43.3)
Unknown	0 (0)	1 (0.8)
PgR Status		
PgR+	25 (42.4)	54 (45.0)
PgR−	33 (55.9)	65 (54.2)
Unknown	1 (1.7)	1 (0.8)
Number of positive lymph nodes		
0	25 (42.4)	47 (39.2)
1–3	18 (30.5)	47 (39.2)
4–9	11 (18.6)	19 (15.8)
≥10	5 (8.5)	7 (5.8)
TNM stage		
I	10 (16.9)	24 (20.0)
II	27 (45.8)	65 (54.2)
III	22 (37.3)	31 (25.8)

A, doxorubucin; C, cyclophosphamide; ECOG, Eastern Cooperative Oncology Group; ER, estrogen status; H, trastuzumab; PLD, pegylated liposomal doxorubicin; PgR, progesterone receptor; T, paclitaxel; BSA, body surface area.

independent data and safety management committee. All patients provided written informed consent. The study is registered at ClinicalTrials.gov (number NCT00550771).

role of the sponsor

Schering-Plough Corporation sponsored this study. The sponsor developed the protocol in conjunction with a number of the investigators, provided clinical study center oversight, supplied study drug, conducted statistical analysis, and participated in manuscript review. Medical writing assistance was provided by the sponsor. All authors reviewed, revised and approved the content of the manuscript.

results

Between August 2007 and April 2009, 181 patients were randomized from 38 centers in Europe, Australia, and Canada. A total of 179 patients were analyzed for safety: 59 in arm A (A + C → T + H) and 120 in arm B (PLD + C + H → T + H) (Figure 1). Demographic and baseline characteristics were balanced; although, there was a numerically higher proportion of patients with >3 positive nodes and stage III disease in arm A (Table 2).

treatment administered

In the ITT population, the mean cumulative anthracycline dose administered was 233 mg/m^2 of doxorubicin and 132 mg/m^2 of PLD. Study treatment was received during cycles 5–8 by 91% of patients in each arm. The same proportion of patients in each arm completed all eight cycles of chemotherapy (88%). The proportion of anthracycline doses requiring modification due to an AE was 6% in the A + C → T + H arm and 16% in the PLD + C + H → T + H arm. Delivered dose intensity was 95% for doxorubicin and 83% for PLD.

Table 3. Cardiac function and toxicity rates in the intent-to-treat population

End point	Arm A (A + C → T + H) (*N* = 59)	Arm B (PLD + C + H → T + H) (*N* = 120)
	No. (%)	No. (%)
Overall incidence of cardiac toxicity (level 1 or 2) or inability to administer trastuzumab (primary end point)	11 (18.6)	5 (4.2)
95% CI[a]	9.7–30.9	1.4–9.5
P-value[b]	0.0036	
During cycles 1–8 of chemotherapy		
Level 1 cardiac toxicity[c]	0 (0)	1 (0.8)
Cardiac deaths	0 (0)	0 (0)
Level 2 cardiac toxicity[d]	3 (5.1)	1 (0.8)
During 1 year of trastuzumab		
Level 1 cardiac toxicity[c]	0 (0)	0 (0)
Level 2 cardiac toxicity[d]	10 (19.2)	4 (3.5)
Hold or suspend trastuzumab due to cardiotoxicity	8 (15.4)	3 (2.6)
LVEF		
Mean baseline LVEF, % (range)	64.4 (55–85)	64.0 (50–85)
Mean absolute LVEF change from baseline to cycle 8, % (range; SD)	−5.6 (−24.0 to +6.0; 6.63)	−2.1 (−17.0 to +15.0; 6.32)
P-value[e]	0.0014	

[a]Computed using the exact binomial method.

[b]Two-tailed Fisher's exact test; the study was not powered to detect differences.

[c]Cardiac death due to heart failure, myocardial infarction or arrhythmia, or probable cardiac death defined as sudden, unexpected death within 24 h of a definite or probable cardiac event, or severe symptomatic heart failure concomitant with a drop in LVEF by >10 percentage points from baseline and to <50% LVEF.

[d]Asymptomatic systolic dysfunction or mildly symptomatic heart failure concomitant with a drop in LVEF by >10 percentage points from baseline and to <50% LVEF.

[e]*P*-values based on an analysis of treatment differences in the change in LVEF from baseline to week 25 adjusting for baseline differences.

A, doxorubicin; C, cyclophosphamide; CI, confidence interval; H, trastuzumab; LVEF, left ventricular ejection fraction; PLD, pegylated liposomal doxorubicin; SD, standard deviation; T, paclitaxel.

cardiac function and toxicity

Cardiac end points are summarized in Table 3. In the ITT population, the overall incidence of cardiac toxicity or inability to administer trastuzumab due to cardiotoxicity (the primary end point) was 18.6% ($n = 11$; 95% CI, 9.7% to 30.9%) in the doxorubicin arm and 4.2% ($n = 5$; 95% CI, 1.4% to 9.5%) in the PLD arm ($P = 0.0036$). These percentages remained the same in the modified ITT population (data not shown). The risk ratio for doxorubicin relative to PLD was 4.4. Of the 16 patients who had an event (11 in the doxorubicin arm versus 5 in the PLD arm), 8 were aged ≥55 years. All of the events occurred after cycle 4. One event met the criteria for level 1 cardiotoxicity, due to a myocardial infarction and subsequent cardiac insufficiency (arm B). Of the remaining 15 events, 7 were due to protocol-defined LVEF criteria (an LVEF drop of >10% to <50% and confirmed in 3–4 weeks), with 3 of the 7 events resulting in clinical symptoms and classified as NYHA class II CHF. The remaining eight events were adjudicated by the independent data and safety management committee, and were all asymptomatic (NYHA class I). No cardiac deaths occurred.

The mean LVEF was comparable between treatment groups at baseline (64.0%, PLD + C + H → T + H and 64.4%, A + C → T + H). The mean absolute reduction in LVEF from baseline to cycle 8 was significantly greater in patients receiving doxorubicin (5.6% versus 2.1%; $P = 0.0014$; Table 3, Figure 2). In the modified ITT population, the mean absolute reduction in the PLD arm was slightly greater at 2.2%.

noncardiac toxic effects

Grades 2–4 noncardiac toxic effects are summarized in Table 4. The most common toxic effects of any grade were alopecia (76.3%), fatigue (61.0%), and nausea (59.3%) in the doxorubicin arm and PPE (66.7%), nausea (52.5%), and alopecia (49.2%) in the PLD arm. Patients in the doxorubicin arm experienced higher rates of alopecia (76.3% versus 49.2%), fatigue (61.0% versus 40.8%), neutropenia (44.1% versus 22.5%), cough (27.1% versus 15.8%), and dizziness (18.6% versus 9.2%). Patients in the PLD arm experienced higher rates of PPE (66.7% versus 5.1%, all grades), rash (29.2% versus 10.2%), dyspepsia (20.0% versus 6.8%), and skin erythema (15.0% versus 3.4%). Febrile neutropenia occurred more often in the doxorubicin arm (8.5% versus 5.0%) with granulocyte colony-stimulating factor as secondary prophylaxis administered to 6 patients (10.2%) receiving doxorubicin and 10 patients (8.3%) receiving PLD.

discussion

The current study observed that trastuzumab given concurrently with PLD plus cyclophosphamide followed by paclitaxel plus trastuzumab appears to be safe from a cardiac standpoint, with a protocol-defined early cardiotoxicity rate that was lower than the comparator regimen of doxorubicin plus cyclophosphamide followed by paclitaxel plus trastuzumab. The overall incidence of cardiac toxicity or inability to administer trastuzumab due to cardiotoxicity, the primary end point, was 18.6% in the doxorubicin arm and 4.2% in the PLD arm despite the concurrent administration of trastuzumab with PLD. Although, this difference was statistically significant, with a *P*-value of 0.0036, it is important to note that the study was not powered to detect significant differences between the two treatment arms. No cardiac deaths occurred on study.

Despite recent controversies surrounding the role of anthracyclines in the adjuvant treatment of breast cancer, these agents remain a cornerstone of therapy. Minimizing anthracycline-associated cardiotoxicity is essential to maximize safety, particularly when used in combination with trastuzumab. Conventional anthracyclines are associated with type I treatment-related cardiac dysfunction characterized by cumulative, dose-dependent direct myocardial injury resulting

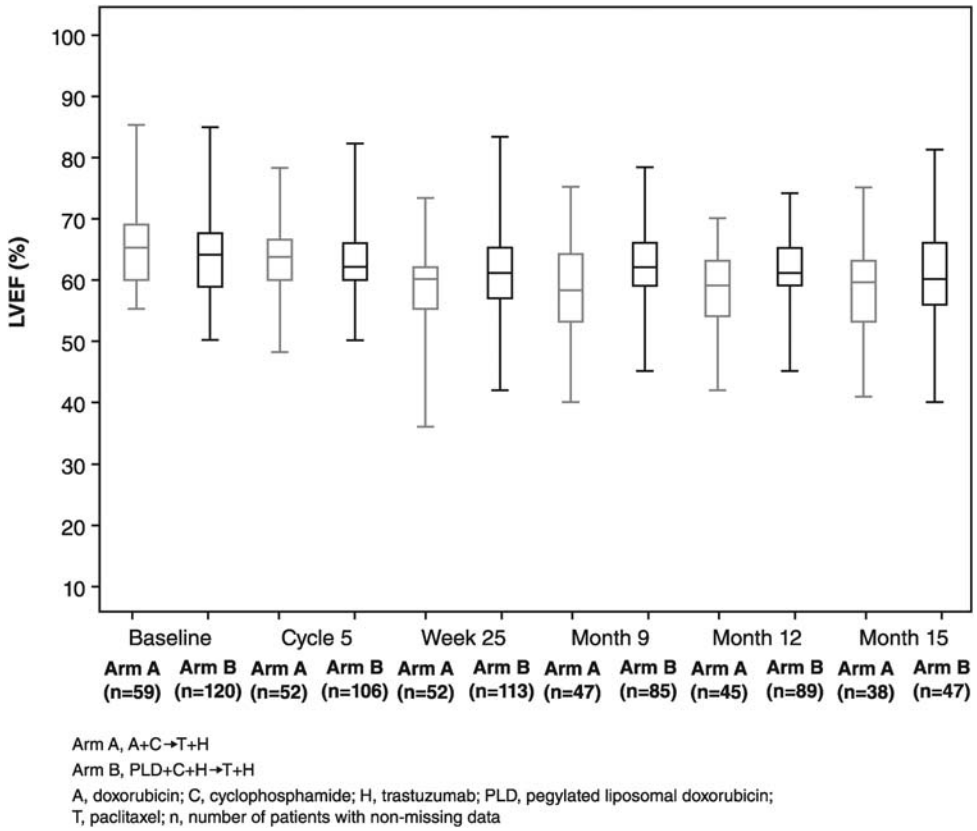

Figure 2. Boxplots of left ventricular ejection fraction over time by treatment arm in the intent-to-treat population.

Table 4. Noncardiac toxic effects

	Arm A (A + C → T + H) (*N* = 59)			Arm B (PLD + C + H → T + H) (*N* = 120)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
	No. (%)					
Any	27 (46)	21 (36)	7 (12)	46 (38)	56 (47)	5 (4)
Nausea	14 (24)	2 (3)	0	20 (17)	0	0
Alopecia						
Grade 1	9 (15)	—		30 (25)	—	
Grade 2	36 (61)	—		29 (24)	—	
Diarrhea	7 (12)	2 (3)	0	9 (8)	0	0
Neutropenia	6 (10)	11 (19)	6 (10)	11 (9)	12 (10)	0
Neuropathy, peripheral	4 (7)	4 (7)	0	6 (5)	4 (3)	0
Mucositis	4 (7)	0	0	18 (15)	3 (2)	0
Asthenia	3 (5)	2 (3)	0	15 (12)	2 (2)	0
PPE	2 (3)	0	—	31 (26)	24 (20)	—
Febrile neutropenia	—	2 (3)	3 (5)	—	5 (4)	1 (1)
Rash	0	0	0	11 (9)	5 (4)	0

A, doxorubicin; C, cyclophosphamide; H, trastuzumab; PLD, pegylated liposomal doxorubicin; PPE, palmar plantar erythrodysesthesia; T, paclitaxel.

in mostly irreversible myocardial injury, while trastuzumab is associated with type II cardiac dysfunction that is dose-independent, characterized by myocyte dysfunction rather than injury, and is predominantly reversible [25]. Liposome encapsulation and pegylation alter the cardiac safety profile of anthracyclines by minimization of drug delivery to normal tissues due to liposomal size, which limits passage through the tight capillary junctions of nonmalignant tissue. This results in the preferential targeting of the wide capillary junctions of malignancy-related vasculature with lessened myocardial

exposure to free doxorubicin resulting in a favorable cardiac safety profile relative to conventional doxorubicin [14, 26]. PLD may therefore lessen anthracycline-induced oxidative stress, as well as diminish the impact of the loss of neuregulin-related cardioprotection induced by trastuzumab, thereby maximizing the cardiac safety of a concurrent anthracycline–trastuzumab regimen [27].

Rates of symptomatic cardiotoxicity are higher with adjuvant trastuzumab compared with non-trastuzumab-containing regimens, although event rates are low (symptomatic/severe event rates for trastuzumab versus non-trastuzumab regimens; 2% versus 0.45% in NSABP-B31/NCCTG and 0.8% versus 0% in HERA) [28, 29]. Most events are reversible with appropriate medical management, although even with prolonged follow-up, recovery is <100%. In the HERA trial, 5.1% of patients discontinued trastuzumab due to cardiac toxicity and in the combined NSABP B-31/NCCTG trials, 6.7% of patients did not begin adjuvant trastuzumab due to an inadequate LVEF post AC chemotherapy, with a further 18.9% discontinuing trastuzumab due to cardiac toxic effects before the planned 1 year of therapy [3, 28]. In the combined analysis, independent risk factors for cardiac toxicity included older age and trastuzumab receipt but these variables did not allow for the identification of a particular population or a baseline LVEF value characterizing increased risk [29].

The current analysis is limited by the short duration of follow-up, the absence of efficacy and quality of life data, and the fact that the study was not powered to detect significant differences between the two arms. As well, each patient could contribute only one event to the primary end point and therefore, the exact distribution of trastuzumab-withdrawal events versus cardiac events could not be determined, although significant overlap would be expected due to the interrelationship between cardiac toxicity and incomplete trastuzumab administration.

Efficacy data are not available from this trial and are needed to fully evaluate the benefit of (i) replacing doxorubicin in the A + C → T + H regimen with PLD and (ii) incorporating trastuzumab concurrent with anthracycline-based chemotherapy earlier in treatment. Non-inferiority of PLD compared with doxorubicin has been established in the metastatic setting, suggesting that replacing doxorubicin should not compromise efficacy [14]. Quality of life data would be important to assess the comparative impact and trade-off between PPE and cardiotoxicity in the PLD versus doxorubicin treatment arms, respectively.

The BACH trial is the first study to specifically examine the safety of a concurrent anthracycline–trastuzumab regimen as adjuvant therapy for HER2 overexpressing breast cancer. Consistent with phase II trials in the metastatic setting indicating that concurrent administration of PLD and trastuzumab is feasible, results from the BACH trial suggest that this strategy is safe, thereby potentially allowing for the earlier incorporation of adjuvant trastuzumab in concurrent treatment protocols [18–22]. The possible clinical benefit of this strategy remains to be defined but would be most ideally examined in a randomized phase III adjuvant trial comparing the current strategy to an optimal non-anthracycline trastuzumab-based regimen such as that under investigation in BCIRG006 [docetaxel–carboplatin–trastuzumab (TCH)].

The cardiac safety analysis of this study suggests that administering trastuzumab concurrent with PLD in the PLD + C + H → T + H regimen is feasible and results in lower rates of early cardiotoxicity and premature cessation of trastuzumab due to cardiotoxicity, compared with A + C → T + H.

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disclosure

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appendix

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Trastuzumab induces antibody-dependent cell-mediated cytotoxicity (ADCC) in HER-2-non-amplified breast cancer cell lines

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Background: Antibody-dependent cell-mediated cytotoxicity (ADCC) mediated by CD56 + natural killer (NK) cells may contribute to the activity of trastuzumab in HER-2-amplified tumours. In this study, we investigated the possibility that trastuzumab might induce ADCC against HER-2-non-amplified breast cancer cells.
Methods: Induction of NK cell-mediated ADCC was examined in trastuzumab-treated HER-2-non-amplified breast cancer cell lines. HER-2 protein levels were also determined in tumour and autologous normal tissue samples from patients with HER-2 negative breast cancer.
Results: Trastuzumab induced a significant ADCC response in the HER-2-amplified HCC1954 and SKBR3 cell lines, and in all five of the non-amplified cell lines, which had low levels of detectable HER-2 by western blot (CAL-51, CAMA-1, MCF-7, T47D, and EFM19). Trastuzumab did not induce ADCC in the K562 control cell line or MDA-MB-468, which has very low levels of HER-2 detectable by enzyme-linked immunosorbent assay (ELISA) only. HER-2 protein was detected by ELISA in 14/15 patient tumour samples classified as HER-2-non-amplified. Significantly lower levels of HER-2 were detected in normal autologous tissue compared with tumour samples from the same patients.
Conclusion: Our results suggest that HER-2-non-amplified breast cancer cells, with low but detectable levels of HER-2 protein, can bind trastuzumab and initiate ADCC.
Key words: ADCC, ERBB2, HER-2 low, HER-2-non-amplified breast cancer, trastuzumab

introduction

HER-2 protein overexpression (>30% of tumour cells, 3 + by immunohistochemistry) or gene amplification (FISH HER-2/CEP7 ratio >2.2), or both, occurs in 20%–25% of breast cancers [1, 2], and is associated with a poorer prognosis [3, 4]. Treatment with trastuzumab, a humanised monoclonal antibody directed against the extracellular domain of the HER-2 protein, prolongs the survival of patients with early stage and metastatic cancers whose tumours have HER-2 gene amplification/protein overexpression [1, 5–8].

The major mechanisms of action of trastuzumab are believed to be abrogation of intracellular HER-2 signalling through pathways including PI3K/Akt and Ras/MAPK leading to cell cycle arrest, reduction in angiogenesis, inhibition of extracellular domain cleavage, and antibody-dependent cell-mediated cytotoxicity (ADCC) [9–13].

Trastuzumab is active in combination with chemotherapy in the HER-2-amplified metastatic disease setting [6, 14] but not in HER-2-non-amplified, non-overexpressed metastatic breast cancer [15]. The improvement in patient outcomes in the metastatic setting led to four major studies in patients with

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