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ORIGINAL REPORT

Dose-Dense Doxorubicin and Cyclophosphamide Followed by Weekly Paclitaxel With Trastuzumab and Lapatinib in HER2/*neu*–Overexpressed/Amplified Breast Cancer Is Not Feasible Because of Excessive Diarrhea

Chau Dang, Nancy Lin, Beverly Moy, Steven Come, Steven Sugarman, Patrick Morris, Alyson Abbruzzi, Carol Chen, Richard Steingart, Sujata Patil, Larry Norton, Eric Winer, and Clifford Hudis

From the Departments of Medicine and of Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY.

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Corresponding author: Chau Dang, MD, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021; e-mail: dangc@mskcc.org.

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ABSTRACT

Purpose
Dose-dense doxorubicin and cyclophosphamide (AC) followed by paclitaxel and trastuzumab (PT) is feasible. Lapatinib is effective in the treatment of human epidermal growth factor receptor 2 (HER2) –positive metastatic breast cancer. We conducted a pilot study of dose-dense AC followed by PT plus lapatinib (PTL) followed by trastuzumab plus lapatinib (TL).

Patients and Methods
Patients with stages I to III, HER2-positive breast cancer and left ventricular ejection fraction (LVEF) of ≥ 50% were enrolled. Treatment consisted of AC (60 mg/m^2 and 600 mg/m^2) for 4 cycles every 2 weeks (with pegfilgrastim 6 mg on day 2) followed by paclitaxel (80 mg/m^2) for 12 doses weekly plus trastuzumab and lapatinib. Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly during paclitaxel then 6 mg/kg every 3 weeks after paclitaxel) and lapatinib (1,000 mg daily) were given for 1 year. The primary end points were feasibility defined as ≥ 80% patients completing the PTL phase without a dose delay/reduction and a cardiac event rate of ≤ 4%.

Results
From March 2007 to April 2008, we enrolled 95 patients. Median age was 46 years (range, 28 to 73 years). At a median follow-up of 22 months, 92 were evaluable. Of the 92 patients, 41 patients (45%) withdrew for PTL-specific toxicities. Overall, 40 (43%) of 92 patients had lapatinib dose reductions, and 27 (29%) of 92 patients had grade 3 diarrhea. Three patients (3%) had congestive heart failure; three patients dropped out because of significant asymptomatic LVEF decline during PTL followed by TL.

Conclusion
Dose-dense AC followed by PTL and then followed by TL was not feasible because of a high rate of lapatinib dose reduction, mostly caused by unacceptable grade 3 diarrhea. Lapatinib (1,000 mg/d) was not feasible combined with weekly PT.

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INTRODUCTION

We previously reported the results of a trial of dose-dense doxorubicin and cyclophosphamide (AC) followed by dose-dense paclitaxel with trastuzumab (PT) in patients with stages I to III breast cancer with overexpression or amplification of the human epidermal growth factor receptor 2 (HER2) and showed that this regimen was feasible, with a congestive heart failure (CHF) rate of 1.4%.[1] This cardiac event (CE) rate was consistent with the larger randomized studies of trastuzumab with chemotherapy in the adjuvant setting.[2-10] In our study, 91% of the patients were able to complete dose-dense chemotherapy with the intended 1 year of trastuzumab. This was better than the 68.6% completion rate reported by the combined analysis of NSABP B-31 (National Surgical Adjuvant Breast and Bowel Project Trial B-31) and N9831 (North Central Cancer Treatment Group Trial 9831) and was comparable to that of HERA (Herceptin Adjuvant Trial).[1-2,7]

Lapatinib, a dual tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR) and HER2, was effective in combination with capecitabine in the treatment of HER2-positive breast cancer in patients who experienced progression after prior anthracycline, taxane, and trastuzumab,

which was the motivating factor for its inclusion in trials for patients with early-stage breast cancer.[11] We chose to specifically test the feasibility of dose-dense chemotherapy combined with dual HER2-targeting agents. We selected dose-dense AC followed by weekly PT plus lapatinib (PTL) to be consistent with one arm of the larger, phase III, adjuvant study (ie, ALTTO [Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization]). We aimed to establish safety data for this larger study. The dose of lapatinib chosen was 1,000 mg daily, which was based on phase I studies that established the feasibility of the combination of trastuzumab and lapatinib (EGF10023) and weekly paclitaxel and lapatinib (EGF10009/EGF105764).[12-13]

Study and Biostatistical Design

This was a phase II trial of dose-dense AC followed by PTL and then TL. Patients received hormonal therapy and radiation as appropriate. The primary objective was to determine the feasibility of this regimen in patients with stages I to III HER2/*neu* overexpressed/amplified breast cancer. Because our focus was on the PTL combination, evaluable patients were those who completed AC and were able to initiate weekly PTL regimen. We used the observed chemotherapy completion rate of greater than 85% from earlier adjuvant trials (without delay or dose reduction) as the target for our feasibility definition.[14-17] We planned to accrue 100 evaluable patients. With this sample size, we had 90% power and 5% type I error to discriminate between true feasibility rates of $\leq$ 67% and 80%. At the end, if 75 or more patients could complete the regimen and if there were four or fewer CEs, then the regimen was considered feasible.

With regard to lapatinib, prolonged corrected QT interval (QTc) was reported in 13 (16%) of 81 patients in an earlier trial.[18] We anticipated that the incidence of prolonged QT would be $\leq$ 20%. This regimen would be feasible if $\geq$ 80% of patients completed the PTL portion without a dose delay/reduction or grade 3 or greater QTc prolongation and if the CE rate was $\leq$ 4%. A CE was defined as cardiac death or symptomatic congestive heart failures (CHF), defined as dyspnea with normal activity or at rest and an absolute decline in left ventricular ejection fraction (LVEF) by greater than 10% to less than 55% or greater than 5% below the lower limit of normal (LLN) of 50% by a multigated acquisition scan (MUGA). The probabilities of stopping the trial for a range of true CE rates are listed in Appendix Table A1 (online only).[19] The secondary end points included an assessment of other toxicities, time to recurrence, overall survival, and an exploratory analysis of serial cardiac biomarkers (troponin I [cTnI] and C-reactive protein [CRP]).

PATIENTS AND METHODS

Patients

Eligible patients had HER2/*neu* immunohistochemistry (IHC) 3+ or fluorescent in situ hybridization (FISH) –amplified breast cancer, regardless of nodal status or tumor size; an absolute neutrophil count $\geq$ 1,000/μL; platelet count $\geq$100,000/μL; normal total bilirubin; and transaminases $\leq$ 2.5 upper limit of normal. Patients could not be on CYP3A4 inducers/inhibitors. An ECG and a normal LVEF by MUGA $\geq$ 50% were required. Patients could not be taking drugs that may prolong the QTc or have grade 3 QTc. Serial MUGA scans were performed at months 2, 6, 9, and 18. Patients with known history of unstable angina, myocardial infarction, CHF, or serious medical illnesses were excluded. This study was approved by the institutional review boards at Memorial Sloan-Kettering Cancer Center and Dana-Farber/Harvard Cancer Center. The CONSORT diagram is presented as Figure 1.

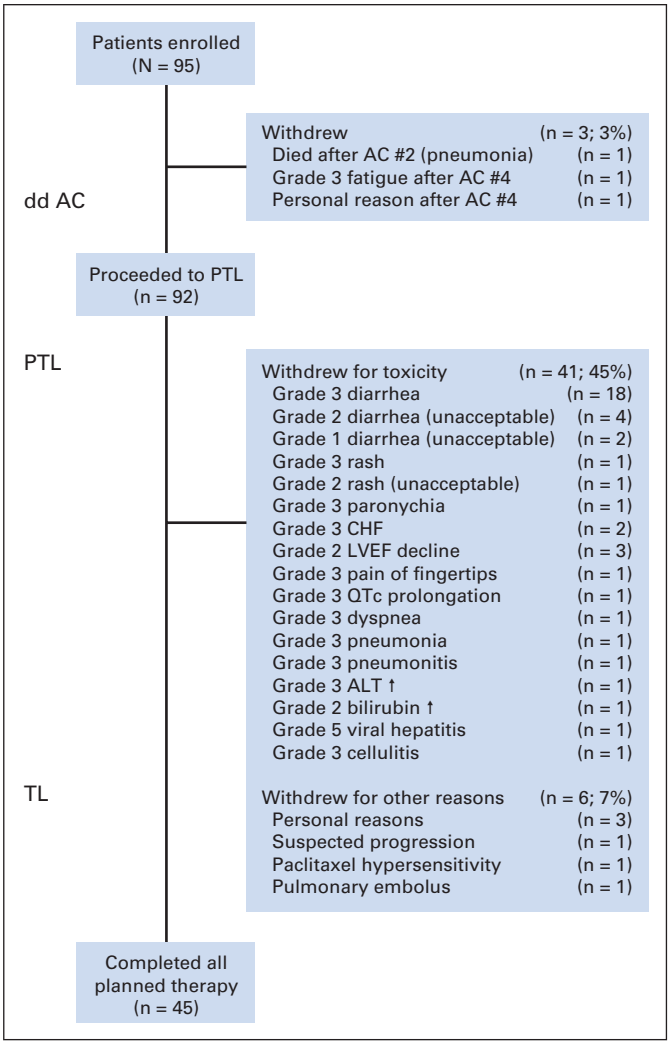

Fig 1. CONSORT diagram. AC, doxorubicin plus cyclophosphamide; dd, dose-dense; PTL, paclitaxel plus trastuzumab plus lapatinib; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; QTc, corrected QT interval; TL, trastuzumab plus lapatinib.

Treatment

Treatment consisted of AC (60mg/m^2 and 600 mg/m^2) for four cycles intravenously (IV) every 2 weeks with pegfilgrastim (6 mg on day 2) followed by paclitaxel (80 mg/m^2) for 12 doses IV weekly continuously (Fig 2). Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly during chemotherapy followed by 6 mg/kg every third week afterward) and lapatinib (1,000 mg orally daily) were started with paclitaxel. Both anti-HER2 therapies were given for a 1-year duration (Fig 2). Trastuzumab and lapatinib were not initiated in those with a post-AC LVEF that declined greater than 15% or $\leq$ 15% but also less than the LLN. Parameters were set for holding both anti-HER2 agents for patients with asymptomatic LVEF declines (Appendix Table A2, online only).

Evaluations During Therapy

Evaluations for complete blood count, liver function test, potassium, magnesium, ECGs, MUGAs, and cTnI and CRP were done at various time points. Time points are outlined in Figure 2.

Toxicity Assessments and Dose Modifications

Toxicities were assessed by the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 3.0. Toxicities are reported separately for AC with paclitaxel, trastuzumab, and lapatinib.

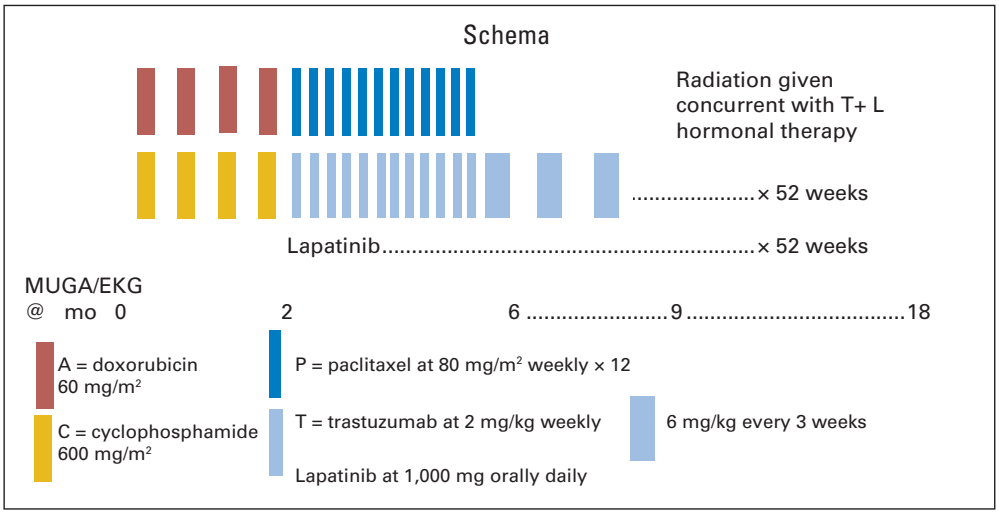

Fig 2. Treatment schema: Complete blood count every 2 weeks during doxorubicin plus cyclophosphamide (AC) followed by paclitaxel plus trastuzumab plus lapatinib (PTL) and every 3 to 6 weeks during trastuzumab plus lapatinib (TL); liver function test every 2 to 4 weeks during AC followed by PTL and every 3 to 6 weeks during TL; magnesium and potassium levels every 3 to 6 weeks during PTL followed by TL; troponin I and C-reactive protein biomarkers every 2 weeks during AC followed by PTL and at months 6, 9, and 18; ECG and multigated acquisition scan (MUGA) at baseline and at months (mo) 2, 6, 9, and 18.

AC and paclitaxel. Patients experiencing neutropenic fever and/or grade 3 or 4 nonhematologic toxicity had day 1 doses in subsequent cycles reduced by 25%. A maximum of two dose reductions were allowed. If, on the day that chemotherapy was due, platelet counts were less than 100,000/μL and/or absolute neutrophil counts were less than 1,000/μL and/or nonhematologic toxicities (excluding alopecia) had not recovered to grade 1 or less, treatment was delayed by up to a week. If a treatment was delayed by greater than 2 consecutive weeks, the patient was taken off study.

Trastuzumab. There was no dose modification for trastuzumab.

Lapatinib. Patients who experienced any grade 3 or a grade 2 or less (ie, unacceptable) toxicity related to lapatinib had this drug held for up to 21 days until grade 1 or less was reached, and one lapatinib dose reduction (1,000 mg to 750 mg) was allowed. If patients had another grade 3 event, then a study withdrawal was mandated. As lapatinib could cause diarrhea and rash, guidelines were in place for the management of these toxicities (Table 1).

Table 1. Protocol-Defined Lapatinib Dose Reduction

Toxicity Type and Grade	Management	Dose Reduction
Diarrhea		
1	None	None
2	Loperamide at first onset	None; if unacceptable, hold ≤ 21 days; resume same dose*
≥ 3	Loperamide at first onset	Hold ≤ 21 days until grade 1 or less; resume at 750 mg daily†
Rash		
1	None	None
2	Minocycline, topical tetracycline, or clindamycin; topical silver sulfadiazine; diphenhydramine; oral prednisone (short course)	None; if unacceptable, hold ≤ 21 days; resume same dose*
≥ 3	Same as in grade 2 event	Hold ≤ 21 days until grade 1 or less; resume at 750 mg daily†

NOTE. Lapatinib starting dose was 1,000 mg daily.
*If dose was held previously for grade 2 toxicity and a grade 2 event recurs, hold ≤ 21 days and reduce to 750 mg daily.
†Only one dose reduction from 1,000 mg to 750 mg daily is allowed. If grade 3 event occurs again at a dose of 750 mg, hold lapatinib and take patient off study.

RESULTS

From March 2007 to April 2008, we enrolled 95 patients. All patients had breast cancer that was HER2/*neu* IHC 3+, FISH amplified, or both. The patient characteristics are listed in Table 2. With a median follow-up of 22 months (range, 18 to 31 months), one (1%) of 95 patients had experienced progression 12 months after therapy completion.

Diarrhea Events, Dose Reductions, and Withdrawals

Overall, three (3%) of 95 patients did not proceed to the PTL phase and were not evaluable (one because of death after AC cycle 2 as a result of viral pneumonia, one because of withdrawal after AC cycle 4 because of grade 3 fatigue, and one because of drop out after AC cycle 4 for personal reasons; Fig 1). In all 95 patients, 84 (88%) experienced diarrhea: 27 patients (28%) had grade 3; 23 (24%) had grade 2; and 34 (36%) had grade 1 events. Of the 92 evaluable patients who entered the PTL phase, 27 (29%) had grade 3 diarrhea, and 22 (24%) and 64 (70%) of patients had diarrhea within the first week and the first cycle of treatment (three doses, once per week, of PT with lapatinib), respectively. Overall, 40 (43%) of 92 patients had a lapatinib dose reduction, mostly because of grade 3 or unacceptable grade 2 or less diarrhea (30 [75%] of 40 patients; Appendix Table A3, online only). Because of a greater than 20% rate of a lapatinib dose reduction, the study was closed with 95 of 100 intended patients enrolled, as specified by the protocol.

Of the 92 evaluable patients, 41 (45%) withdrew from the study for toxicities related to PTL followed by TL, mostly because of grade 3 or unacceptable grade 2 or less diarrhea despite active diarrhea management (24 [59%] of 41 patients; Fig 1). Of these 24 patients, 23 dropped out during the PTL phase, and one withdrew during the TL phase because of diarrhea. Six (7%) of 92 evaluable patients withdrew from the study for other reasons (Fig 1).

Rash Events, Dose Reductions, and Withdrawals

The grades 1, 2, and 3 event rates for rash were 18%, 5%, and 4%, respectively. The grades 1, 2, and 3 event rates for acneiform rash were 12%, 2%, and 2%, respectively (Table 3). In the 92 evaluable patients,

Table 2. Patient Demographics and Clinical Characteristics

Characteristic	Patients (N = 95) No.	%
Age, years		
Median	46	
Range	28-73	
< 40	20	21
40-49	37	39
50-59	29	31
60-69	8	8
≥ 70	1	1
Tumor size, cm		
≤ 2	38	40
2.1-5	39	41
> 5	1	1
Occult primary	1	1
Unknown (neoadjuvant)	16	17
No. of involved nodes		
0	15	16
1-3	39	41
4-9	14	15
≥ 10	11	11
Unknown (neoadjuvant)	16	17
Receptor status		
ER/PR positive	43	45
ER positive/PR negative	10	11
ER negative/PR positive	0	0
ER/PR negative	42	44
Surgical treatment		
Lumpectomy	36	38
MRM	58	61
Both lumpectomy and MRM	1	1
Radiation		
Breast/chest*	74	78
Left sided	37	50
Right sided	36	49
Bilateral	1	1

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; MRM, modified radical mastectomy.
*Numbers and percentages of patients for radiation sides is based on a total of 74 patients who received breast/chest radiation.

Table 3. Hematologic and Nonhematologic Toxicities

Toxicity	Patients by Toxicity Grade (N = 95) 1 No.	%	2 No.	%	3 No.	%	4 No.	%
Febrile neutropenia	—		—		1	1	—	
Leukopenia	23	24	30	32	5	5	2	2
Neutropenia	3	3	16	17	5	5	4	4
Anemia	40	42	47	50	2	2	0	0
Thrombocytopenia	24	25	1	1	0	0	0	0
Diarrhea	34	36	23	24	27	28	0	0
Rash	17	18	5	5	4	4	0	0
Acneiform rash	11	12	2	2	2	2	0	0
Pruritus	18	19	1	1	1	1	0	0
Fatigue	44	46	39	41	8	8	1	1
Fever without neutropenia	25	26	3	3	1	1	0	0
Nausea	53	56	15	16	2	1	1	1
Emesis	10	11	6	6	1	1	0	0
Dyspepsia	15	16	2	2	1	1	0	0
Mucositis	47	50	12	13	0	0	0	0
Constipation	46	48	8	8	0	0	0	0
Headache	24	25	6	6	1	1	0	0
Dizziness	9	10	1	1	0	0	0	0
Dyspnea	34	36	3	2	2	2	0	0
Sensory neuropathy	49	52	12	13	3	3	0	0
Nail changes	20	21	7	7	0	0	0	0
Pain, arthralgia	18	19	1	1	0	0	0	0
Pain, myalgia	9	10	2	2	0	0	0	0
AST	58	61	5	5	2	2	1	1
ALT	44	46	15	16	4	4	1	1
Alkaline phosphatase	40	42	0	0	0	0	0	0
Bilirubin	10	11	4	4	0	0	1	1

three patients (3%) had grade 3 rash, and four patients (4%) had grade 2 unacceptable rash, which required a lapatinib dose reduction (Appendix Table A3). Only one patient (1%) with grade 3 rash and one patient (1%) with grade 2 unacceptable rash withdrew from study for these reasons (Fig 1).

Cardiac Outcomes

The median LVEFs were as follows: at baseline, 68% (range, 52% to 81%; n = 95); at month 2, 69% (range, 47% to 81%; n = 93); at month 6, 65% (range, 24% to 80%; n = 89); at month 9, 65% (range, 45% to 76%; n = 76); and at month 18, 65% (range, 30% to 78%; n = 30; Fig 3). One patient had an asymptomatic LVEF decline to 47% at month 2 after dose-dense AC by a MUGA scan done at a local institution. As per study, anti-HER2 therapies were not started, and a repeat MUGA was done 4 weeks later that showed an LVEF of 64%. Thus, this patient was then allowed to start her anti-HER2 therapies.

Overall, three (3%) of 95 patients (95% CI, 0.7% to 9.0%) had CHF (Fig 3). One patient had CHF at month 3 (LVEF of 68% at baseline, 68% post AC, and 48% at month 3). She was given a diuretic and an angiotensin-converting enzyme inhibitor. Trastuzumab was held permanently, and the patient never started lapatinib. A second patient developed CHF at month 6 (LVEF of 52% at baseline, 56% after dose-dense AC, and 24% at month 6), and both anti-HER2 therapies were held permanently. The patient was started on digoxin, a beta blocker, an alpha blocker, and a diuretic. Her last LVEF was 28% at 12 months after the event. The third patient developed CHF at month 12 (LVEF of > 70% at baseline, > 70% after AC, 62% at month 6, 58% at month 10, and 25% at month 12). She was given a diuretic, a beta blocker, an alpha blocker, and an angiotensin-converting enzyme inhibitor. Trastuzumab was held permanently. This patient had a short course of lapatinib, which was stopped at month 3.5 because of unacceptable grade 1 diarrhea. Her LVEF was still low at 30% at 6 months after the event. There were no cardiac deaths on this study.

Significant asymptomatic LVEF declines occurred in six (7%) of 92 evaluable patients, which resulted in a hold of the anti-HER2 therapies. Two patients dropped out because of persistent asymptomatic LVEF declines at months 4 and 8, respectively. One patient had dropped out earlier at month 3 because of grade 3 diarrhea, but she continued on trastuzumab; she later did not continue trastuzumab because of persistent asymptomatic LVEF decline at month 7. Three (3%) of 92 patients had a recovery of the LVEF, and anti-HER2 therapies were reinstituted. The grade 3 QTc prolongation occurred in two (2%) of 92 evaluable patients; one patient withdrew for this reason (Fig 1), and one was hospitalized (Appendix Table A4, online only).

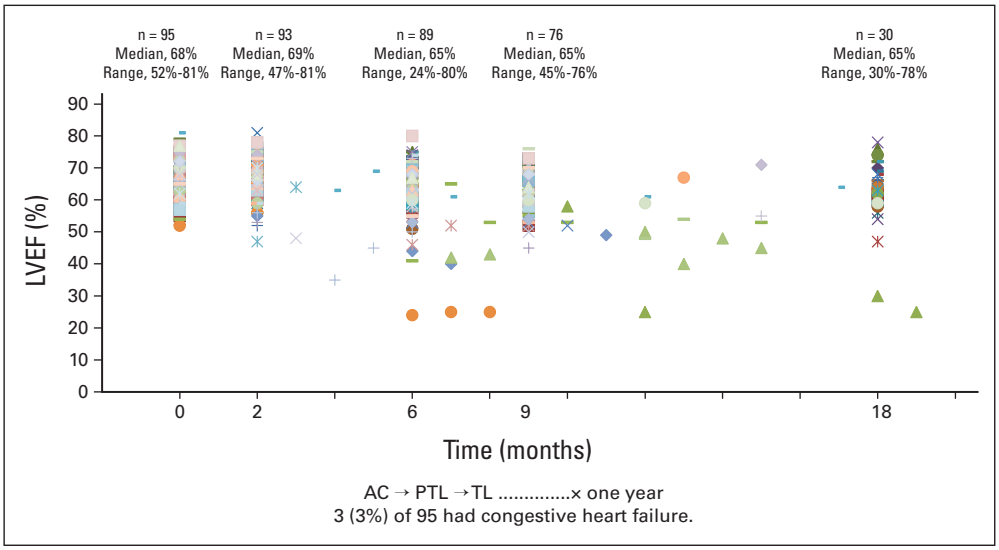

Fig 3. Left ventricular ejection fraction (LVEF) results. AC, doxorubicin plus cyclophosphamide; PTL, paclitaxel plus trastuzumab plus lapatinib; TL, trastuzumab plus lapatinib.

Nonhematologic and Hematologic Toxicities

The nonhematologic and hematologic toxicities are summarized in Table 3. The toxicities were as expected.

Hospitalizations

There were 32 hospitalizations in 23 of 95 patients (24%). These events are noted on Appendix Table A4.

DISCUSSION

Our phase II study of AC followed by weekly paclitaxel with trastuzumab and lapatinib was not feasible with a lapatinib dose of 1,000 mg daily because of excessive diarrhea. With a median follow-up of 22 months, 43% of patients required a lapatinib dose reduction; thus, the study was closed early. Furthermore, 45% withdrew from study because of toxicities related to PTL followed by TL, mainly because of grade 3 or grade 2 or less unacceptable diarrhea. The overall incidence of all-grade diarrhea was 88%, and 29% of patients experienced the highest grade of this toxicity as grade 3 diarrhea during the PTL phase. Johnson et al[20] reported the Mayo Clinic experience with AC followed by PTL (ie, a similar schedule as in our study) and found that 33 (43%) of 77 patients who completed AC had grade 3 or greater diarrhea. This led to the implementation of a more aggressive diarrhea management. Similarly, Guarneri et al[21] reported the result of the neoadjuvant trial CHERLOB (Chemotherapy Plus Trastuzumab, Lapatinib or Both in HER2-Positive Operable Breast Cancer), in which patients were randomly assigned to A (PT followed by FEC + trastuzumab) versus B (PL followed by FEC + lapatinib) versus C (PTL followed by FEC + TL). The dose of lapatinib was also 1,000 mg daily in arm C, and the paclitaxel schedule was weekly. The grade 3 or greater diarrhea rate was 41% in arm C. The diarrhea rates for these two studies were similar together but higher than ours. One possible explanation for the lower grade 3 diarrhea rate in our study could be that the institution of proactive diarrhea management was early in our trial.

These event rates were much higher than the less than 10% grades 3 to 4 diarrhea rate reported in an analysis by Crown et al[22] of patients in 11 studies who were treated with lapatinib as monotherapy or in combination with capecitabine or the taxanes. The incidence of all-grade diarrhea was 51% among patients treated with lapatinib monotherapy, and it was 65% in those treated with lapatinib and capecitabine.[22] However, in two phase I studies with the taxanes, there was a higher incidence of all-grade diarrhea in EGF10009 (with lapatinib at 1,250 to 1,500 mg daily and with paclitaxel at 135 to 225 mg/m^2 every 3 weeks or 80 mg/m^2 weekly) and in EGF10021 (with lapatinib at 1,000 to 1,500 mg daily and with docetaxel at 50 to 75 mg/m^2 every 3 weeks); incidences were 82% and 71%, respectively.[22] This was similar to our finding, likely because of the pharmacokinetic (PK) interaction between the taxanes and lapatinib. Crown et al[13] reported that the PK analysis of paclitaxel (every 3 weeks) and lapatinib in EGF10009 showed that the area under the curve was increased by greater than 20% for both lapatinib and paclitaxel. In EGF10009, the incidence of grade 3 or greater diarrhea was higher in those on lapatinib combined with paclitaxel given weekly (six of 12 patients, or 50%) than for those on the regimen every 3 weeks (three of 44 patients, or 7%). Subsequently, proactive diarrhea management was instituted; in EGF105764 (with lapatinib plus weekly paclitaxel), the incidence of grade 3 or greater diarrhea was less (three of 53 patients, or 6%).[13] However, in our study, despite proactive diarrhea management and use of a lower dose of lapatinib (1,000 mg daily) with trastuzumab, established by Storniolo et al,[12] and with weekly paclitaxel, the grade 3 diarrhea was excessive at 29%. There are a few explanations. First, all three drugs individually can cause diarrhea, but most events are grades 1 or 2.[18,23-24] Additionally, chemotherapy agents, including paclitaxel, may exert a cytotoxic effect on the intestinal crypt cells to cause a loss in absorption and, thus, possibly worsen the diarrhea effects from lapatinib.[25] An ongoing phase III study, EGF104383, comparing PTL with PT plus placebo in the metastatic setting showed a high rate of grade 3 diarrhea (seven of 15 patients).[26] Second, there is more grade 3 diarrhea reported with paclitaxel given weekly than given every 3 weeks.[23] Our observation suggests that it is important to conduct a PK analysis of lapatinib with the weekly schedule of paclitaxel.

In our study, 24% of patients had diarrhea within the first week of lapatinib exposure, similar to a 37% rate within 6 days in the pooled

analysis.[22] Furthermore, 70% of the patients experienced diarrhea within the first cycle of PTL, which was similar to the 60% rate reported by the Mayo Clinic study.[20] The mechanism of lapatinib-related diarrhea is not clearly defined. However, it is known that diarrhea is a common toxicity of other EGFR inhibitors alone (ie, cetuximab, gefitinib, erlotinib, and neratinib) in the order of 25% to 50%, and the incidence is increased dramatically in combination with cytotoxic drugs to greater than 70%.[27-29] In our study, patients were not allowed to be on CYP3A4 inducers or inhibitors, as lapatinib is metabolized through this enzyme system. In the future, it may be worthwhile to study the variations in CYP3A4 expression in our patient population to additionally elucidate why some patients had more diarrhea than others. For now, when patients do experience diarrhea, the American Society of Clinical Oncology guidelines for the management of this adverse event should be followed.[30]

In terms of cardiac toxicity, we report a symptomatic CHF incidence of 3% in our study, which is similar to a rate of 2% reported by the Mayo Clinic study.[20] Perez et al[31] recently reviewed the data across 44 studies on 3,689 patients on lapatinib who were previously treated with an anthracyline, trastuzumab, or neither. In this review, the symptomatic CHF rate was 0.2% and the asymptomatic CE rate was 1.4%. Our symptomatic CHF rate of 3%, which was higher than what was reported with dose-dense AC followed by PT[1] and in the Perez et al[31] review, could be due to the enhanced cardiac toxicity of lapatinib and trastuzumab given concurrently. Notably, Blackwell et al[32] reported a higher CE rate in those treated with both lapatinib and trastuzumab versus lapatinib alone. Thus, there may be the potential for greater cardiac toxicity from these two drugs in combination. In terms of asymptomatic CEs, six (7%) of 92 patients had interruptions in anti-HER2 therapy because of significant asymptomatic LVEF declines, and three (3%) of 92 patients had appropriate LVEF recovery within 4 weeks and were able to restart treatment. These results were similar to the asymptomatic CE rate previously reported for dose-dense AC followed by PT.[1] Grade 3 QTc prolongation only occurred in 2% of the patients. We will be reporting the results of the correlative biomarkers (cTnI and CRP) in a separate manuscript.

Overall, this study is important, because it has demonstrated an expectedly high rate of grade 3 diarrhea. Along with the results of the Mayo Clinic trial, this has led to a modification of one arm of the ALTTO study (ie, lapatinib is now reduced to 750 mg daily when combined with PT). As we strive to improve outcomes through the addition of new targeted agents, it remains critically important to establish feasibility and provide guidance for the management of toxicities through phase II studies.

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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AUTHOR CONTRIBUTIONS

Conception and design: Chau Dang, Carol Chen, Richard Steingart, Sujata Patil, Larry Norton, Eric Winer, Clifford Hudis

Administrative support: Chau Dang, Nancy Lin, Beverly Moy, Steven Come, Steven Sugarman, Alyson Abbruzzi, Larry Norton, Eric Winer, Clifford Hudis

Provision of study materials or patients: Chau Dang, Nancy Lin, Beverly Moy, Steven Come, Steven Sugarman, Larry Norton, Eric Winer, Clifford Hudis

Collection and assembly of data: Chau Dang, Nancy Lin, Beverly Moy, Steven Come, Steven Sugarman, Patrick Morris, Alyson Abbruzzi, Carol Chen, Richard Steingart, Sujata Patil, Larry Norton, Eric Winer, Clifford Hudis

Data analysis and interpretation: Chau Dang, Nancy Lin, Beverly Moy, Steven Come, Steven Sugarman, Patrick Morris, Alyson Abbruzzi, Carol Chen, Richard Steingart, Sujata Patil, Larry Norton, Eric Winer, Clifford Hudis

Manuscript writing: Chau Dang, Nancy Lin, Beverly Moy, Steven Come, Steven Sugarman, Patrick Morris, Carol Chen, Richard Steingart, Sujata Patil, Larry Norton, Eric Winer, Clifford Hudis

Final approval of manuscript: Chau Dang, Nancy Lin, Beverly Moy, Steven Come, Steven Sugarman, Patrick Morris, Alyson Abbruzzi, Carol Chen, Richard Steingart, Sujata Patil, Larry Norton, Eric Winer, Clifford Hudis

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