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Significantly Higher Pathologic Complete Remission Rate After Neoadjuvant Therapy With Trastuzumab, Paclitaxel, and Epirubicin Chemotherapy: Results of a Randomized Trial in Human Epidermal Growth Factor Receptor 2–Positive Operable Breast Cancer

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ABSTRACT

Purpose
The objective of this study was to determine whether the addition of trastuzumab to chemotherapy in the neoadjuvant setting could increase pathologic complete response (pCR) rate in patients with human epidermal growth factor receptor 2 (HER2) –positive disease.

Patients and Methods
Forty-two patients with HER2-positive disease with operable breast cancer were randomly assigned to either four cycles of paclitaxel followed by four cycles of fluorouracil, epirubicin, and cyclophosphamide or to the same chemotherapy with simultaneous weekly trastuzumab for 24 weeks. The primary objective was to demonstrate a 20% improvement in pCR (assumed 21% to 41%) with the addition of trastuzumab to chemotherapy. The planned sample size was 164 patients.

Results
Prognostic factors were similar in the two groups. After 34 patients had completed therapy, the trial's Data Monitoring Committee stopped the trial because of superiority of trastuzumab plus chemotherapy. pCR rates were 25% and 66.7% for chemotherapy (n = 16) and trastuzumab plus chemotherapy (n = 18), respectively ($P = .02$). The decision was based on the calculation that, if study continued to 164 patients, there was a 95% probability that trastuzumab plus chemotherapy would be superior. Of the 42 randomized patients, 26% in the chemotherapy arm achieved pCR compared with 65.2% in the trastuzumab plus chemotherapy arm ($P = .016$). The safety of this approach is not established, although no clinical congestive heart failure was observed. A more than 10% decrease in the cardiac ejection fraction was observed in five and seven patients in the chemotherapy and trastuzumab plus chemotherapy arms, respectively.

Conclusion
Despite the small sample size, these data indicate that adding trastuzumab to chemotherapy, as used in this trial, significantly increased pCR without clinical congestive heart failure.

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INTRODUCTION

Systemic therapy is an integral part of the multidisciplinary curative treatment of primary breast cancer and results in significant reductions in risk of recurrence and death.[1-3] Combination chemotherapy regimens administered as postoperative adjuvant therapy

are superior to single-agent chemotherapy, and anthracycline-containing regimens are superior to nonanthracycline-containing combinations. Primary induction chemotherapy has been evaluated in a number of studies in patients with breast cancer.[4] Randomized studies indicated that the survival benefit from particular treatment regimens is similar, regardless of whether the treatment is administered preoperatively or postoperatively. A practical benefit of preoperative therapy is that it will downstage the primary tumor in most women, allowing a higher rate of breast preservation. It also provides an in vivo assessment of tumor response to the particular drug regimen and, hence, an opportunity to optimize therapy.[5] Furthermore, pathologic complete response (pCR) after preoperative therapy is a powerful surrogate of long-term disease-free survival. It is hypothesized that a regimen that produces higher rates of pCR in the neoadjuvant treatment setting will also result in higher rates of long-term cure.

Human epidermal growth factor receptor 2 (HER2) is overexpressed in 25% to 30% of breast cancers, suggesting a role for overexpression in tumorigenesis.[6] This overexpression is most commonly the result of gene amplification. Several lines of evidence support the role of HER2 overexpression in the pathogenesis and poor clinical outcome of human tumors. A number of these studies have shown that breast cancers that overexpress HER2 have a more aggressive course and higher relapse and mortality rates. HER2 overexpression in retrospective analyses of adjuvant studies was also associated with resistance to cyclophosphamide, methotrexate, and fluorouracil chemotherapy.[7,8] With regard to response to hormonal therapies and anthracycline-based chemotherapy, the role of HER2 overexpression is unclear.[9,10]

Trastuzumab (Herceptin; Genentech Inc, South San Francisco, CA) is a humanized monoclonal antibody directed against the extracellular domain of HER2.[11] Trastuzumab as a single agent has modest antitumor activity.[12-14] In phase III randomized trials, trastuzumab in combination with standard chemotherapy (paclitaxel, docetaxel or doxorubicin, and cyclophosphamide combinations) demonstrated improvement in time to progression, overall response, and duration of response and a favorable impact on survival compared with the same chemotherapy alone as therapy for metastatic breast cancer overexpressing HER2.[15-17] Cardiac dysfunction was observed in 27% of patients treated with trastuzumab and anthracycline-based combination therapy.[15] No randomized preoperative study has been performed with trastuzumab. Given the enhanced antitumor activity in these studies, we designed a study in which patients with HER2-positive operable breast cancer were randomly assigned to either chemotherapy (sequential paclitaxel and fluorouracil, epirubicin, and cyclophosphamide [FEC]) with simultaneous weekly trastuzumab for 24 weeks or chemotherapy alone. The choice of chemotherapeutic agents was based on what we consider to be among the most active agents in breast cancer. The goal of the study was to demonstrate that the addition of trastuzumab to a complete 6-month preoperative chemotherapy regimen will increase pCR rate two-fold compared with chemotherapy alone. We selected epirubicin as part of the combination regimen in an effort to reduce cardiac toxicities compared with those attributed to trastuzumab and doxorubicin combination. The results of this prospective randomized phase III study were recently presented,[18] and complete results are included in this article.

PATIENTS AND METHODS

Patients with histologically confirmed invasive, but noninflammatory, carcinoma of the breast with stage II to IIIA disease were included in this study. Histologic confirmation of invasive tumor was performed by core needle biopsy. Fine-needle aspiration of clinically suspicious lymph nodes was performed. All tumors were HER2 positive by fluorescence in situ hybridization (FISH) or showed 3+ overexpression by immunohistochemistry. Before initiation of therapy, all patients underwent staging evaluation, which included a complete history, physical examination, CBC, chemistry profile, chest radiograph, ultrasound or computed tomography scan of the liver, and a bone scan. Mammography of both breasts was performed, and additional breast and axillary assessment of the tumor site was conducted by ultrasound. Before entry onto the study, each patient was informed about the investigational nature of the study, and a written informed consent, which was approved by the institutional review board, was obtained. All patients were required to have adequate bone marrow function as defined by an absolute granulocyte count of more than 1,500/μL and platelet count of more than 100,000/μL. Patients had to have adequate liver function, with bilirubin within normal laboratory values. In addition, patients had to have adequate renal function, which was defined as serum creatinine less than 2.5 mg/100 mL. Cardiac evaluation included a baseline echocardiogram or a cardiac scan. Patients with a history of uncompensated congestive heart failure or a cardiac ejection fraction less than 45% were excluded. Each patient was reviewed in a multidisciplinary conference with designation of whether breast conservation was a reasonable surgical option before treatment was initiated.

All patients were prospectively registered into our central research database. Patients were randomly assigned to receive either chemotherapy alone or the same chemotherapy with trastuzumab on a weekly basis for 24 weeks. Patients had a physical examination of breasts and regional lymph node basins before each cycle of chemotherapy. Antitumor activity was evaluated with imaging studies after four cycles of chemotherapy (at the completion of paclitaxel) and before surgery (at the completion of FEC). Tumor measurements were documented after the first 12 weeks of paclitaxel and at the completion of FEC therapy to determine the best clinical response before local therapy. CBCs, differential counts, and platelet counts were repeated weekly to monitor the myelotoxicity of chemotherapy in the first cycle, and subsequently, blood counts were performed on day 1 of each cycle. Cardiac evaluation was performed at baseline and then repeated after completion of paclitaxel and then again at the completion of FEC therapy. If there was a marked response to chemotherapy after one or more cycles of chemotherapy, the tumor site was

marked with a stainless steel marker placed under ultrasound guidance. Follow-up ultrasound and mammography were performed after four cycles of paclitaxel and again after four cycles of FEC. After completion of chemotherapy and surgical and/or radiation therapy, patients with estrogen receptor (ER) –positive and/or progesterone receptor–positive tumors received adjuvant endocrine therapy. Patients were evaluated at 4-month intervals during the initial 2 years and then at 6-month intervals for the third year. Mammograms were performed yearly.

Clinical complete remission was defined as disappearance of all clinical evidence of active tumor per evaluation by physical examination. Partial response was defined as equal or greater than 50% decrease in measurable lesions for a minimum of 4 weeks as determined by the product of the longest perpendicular diameters of the lesion(s). Minor response was defined as a decrease in the tumor size that did not qualify for partial response, and progressive disease was defined as any increase in tumor size or appearance of new lesions. pCR was defined as no evidence of residual invasive cancer, both in breast and axilla.

The primary objective of the study was to compare pCR rates between the two arms. The projected pCR rate with the standard arm was estimated to be 21% based on previous experience with similar chemotherapy.[19] The study was powered to detect a 20% improvement in the pCR rate (ie, from 21% to 41%). Accrual of 164 patients was planned. With this number of patients, the study would have had 80% power to detect a 20% difference (two-sided type I error = 0.05). Patients were assigned to treatment arms using a stratified blocked randomization, with strata based on age (< 50 years $v \geq 50$ years) and stage of disease. One interim analysis was planned when pCR results were known for the first 82 patients. Stopping rules were provided in the event that accumulating evidence indicated a rate of cardiac toxicity more than 3%. All patients were included in the analysis of response and toxicity. Toxicities were tabulated by type and grade using the National Cancer Institute Common Toxicity Criteria, Version 2.0. Toxicity and response rates were compared using the χ^2 test. In view of the apparently high pCR rate in the trastuzumab plus chemotherapy arm, the data were presented to the M.D. Anderson Data Monitoring Committee (DMC). The DMC requested information on the patient accrual rate, response, and adverse events by treatment. The DMC also requested an analysis based on Bayesian predictive probabilities,[20,21] addressing the question of how likely the final results of the study (ie, after the full planned sample size of 164 patients) would show statistical significance favoring the trastuzumab plus chemotherapy arm.

Chemotherapy

Each patient was to receive four cycles of paclitaxel followed by four cycles of FEC. Paclitaxel was administered at 225 mg/m^2 as a 24-hour continuous intravenous (IV) infusion; cycles were repeated every 3 weeks for four cycles. Each patient was premedicated with either dexamethasone 20 mg orally, 12 and 6 hours before administration of paclitaxel, or dexamethasone 20 mg IV 30 minutes before chemotherapy. Patients received diphenhydramine 50 mg IV and cimetidine 300 mg IV 30 minutes before paclitaxel infusion. The dose and schedule of paclitaxel was selected based on information available at the time of study inception in 1999. At that time, the optimal dose and schedule of paclitaxel was unclear, and there were data to suggest that a 24-hour continuous infusion and somewhat higher doses might be beneficial compared with short infusion.[22,23] These assumptions today do not seem to be validated. On the basis of current evidence, the most effective schedule may be weekly administration.[19,24] FEC consisted of fluorouracil 500 mg/m^2 IV on days 1 and 4, cyclophosphamide 500 mg/m^2 IV on day 1 only, and epirubicin 75 mg/m^2 on day 1 only. Patients randomly assigned to the trastuzumab arm of the study received trastuzumab at a dose of 4 mg/kg IV on day 1 of the first treatment cycle, administered over 90 minutes. Subsequent doses of weekly trastuzumab were administered at a dose of 2 mg/kg over 30 minutes. Patients were monitored for 1 hour after the first infusion and for 30 minutes after subsequent infusions. Trastuzumab was administered before chemotherapy. A total of 24 doses of trastuzumab were administered on a weekly basis. In the first cycle, trastuzumab was administered 1 day before paclitaxel to monitor any potential infusion reaction; on subsequent courses, therapies were administered on the same day if there was no adverse event with the first cycle. After completion of 24 weeks of systemic therapy, patients received local therapy. After completion of systemic and local therapy, patients with ER-positive tumors received tamoxifen at a dose of 20 mg daily or anastrozole 1 mg daily if the patient was postmenopausal. This was planned for 5 years, regardless of the menopausal status of the patient.

Dose Modification Criteria

The dose of paclitaxel was reduced by 50% in subsequent cycles if a patient developed grade 3 neurotoxicity. Patients were required to have more than 1,500/μL granulocytes and more than 100,000/μL platelets before the administration of the next cycle of chemotherapy. Doses of the chemotherapy drugs (both FEC and paclitaxel) were not altered if the patient's lowest granulocyte count was more than 250/μL, there was no other organ toxicity greater than grade 2, and the lowest platelet count was more than 50,000/μL. Patients did not receive prophylactic hematopoietic growth factor unless neutropenic fever occurred. If a patient experienced neutropenic fever, either on the paclitaxel or the FEC phase of therapy, granulocyte colony-stimulating factor was added to the treatment at 5 μg/kg on days 5 through 18 or until the granulocyte count was more than 2000/μL, and chemotherapy dose was not modified. In subsequent cycles, if a patient experienced fever after the addition of granulocyte colony-stimulating factor, the dose of the drug(s) was reduced by 20%. The dose of the drug(s) was reduced by 20% if a patient experienced organ toxicity other than myelosuppression of grade ≥ 3.

Local Therapy

After completion of neoadjuvant therapy, each patient was evaluated. Patients who were considered appropriate candidates for breast conservation therapy (BCT) were offered segmental mastectomy (lumpectomy). Patients who were considered inappropriate for BCT or who did not desire BCT underwent total mastectomy. All patients (mastectomy and BCT) with persistent axillary disease detected by physical examination or by ultrasonography and verified by ultrasound-guided fine-needle aspiration underwent axillary lymph node dissection. Patients who were clinically node-negative after neoadjuvant therapy proceeded to lymphatic mapping and sentinel lymph node biopsy. Clinically node-negative patients who showed microscopic residual disease in the sentinel lymph node(s) were recommended for axillary lymph node dissection, although some elected to receive postoperative radiation therapy to the regional lymph nodes instead.

All patients treated with a segmental mastectomy received whole-breast irradiation. The breast was treated with standard medial and lateral tangent fields using 6 to 15 MV photons to a

total dose of 50 Gy delivered in 25 fractions. Subsequently, the tumor bed was treated with an additional 10 Gy in five fractions with electrons. Regional nodal irradiation to the supraclavicular fossa-axillary apex was used in patients with clinical stage III disease, in patients with four or more positive lymph nodes, and in selected patients with one to three positive lymph nodes. Radiation treatments were not offered to patients with initial clinical stage II breast cancer who were treated with mastectomy and had negative lymph nodes. Radiation treatment of the chest wall and draining lymphatics was used for patients with stage III disease, patients with four or more positive lymph nodes, and selected patients with one to three positive lymph nodes. In these patients, the chest wall was typically treated with opposed lateral tangent fields matched to a medial electron field that included the internal mammary lymph nodes and a separate matched photon field that treated the supraclavicular fossa-axillary apex. These regions were treated to 50 Gy in 25 fractions with a subsequent 10 Gy boost to the chest wall and areas of unresected, initially positive, adenopathy.

Pathologic Evaluation

After chemotherapy, resected specimens were evaluated by breast pathologists using the standard protocol of The M.D. Anderson Cancer Center.[25,26] In brief, the surgeon oriented the specimen with sutures and accompanied it to the pathology suite. In cases showing significant clinical response, the breast resection specimen was radiographed to identify metallic markers, which were placed under ultrasound examination before chemotherapy. The specimen was inked using multiple colors to identify each face of the specimen. It was then sectioned into 3- to 5-mm slices. The sliced specimen was radiographed, and a radiologist reviewed the films to determine the presence and extent of residual tumor. The pathologist examined the sliced specimen grossly to identify suspicious areas and note their proximity to margins. The radiographic and pathologic evaluations were discussed with the surgeon who decided whether additional margin should be obtained or not. Permanent paraffin sections of the suspicious areas and margins were obtained. The number of sections taken was based on the gross inspection, radiographic features, and size of the resection specimen. The entire radiographic abnormality as well as firm and suspicious-appearing breast tissue was submitted for histologic evaluation. In general, for nonpalpable (clinical complete response) cases, at least 10 to 15 blocks were examined to assess the presence of residual microscopic disease. In cases with residual palpable mass (partial clinical response or no response), the resection specimen was inked and sectioned into 3- to 5-mm slices. The pathologist examined the slices and determined the tumor size and gross evaluation and confirmed the tumor size by microscopic evaluation. The largest area of residual disease was included to document the extent of disease in a patient with multiple foci of persistent invasive cancer. All axillary lymph nodes were also carefully evaluated by serial gross sectioning. One or two representative histologic sections were evaluated for lymph nodes that contained grossly identifiable metastatic carcinoma. Lymph nodes that did not show grossly identifiable tumor were submitted for histologic evaluation in their entirety. One representative histologic section was evaluated per paraffin block. Immunohistochemical staining for cytokeratin was not routinely performed on negative nodes.

RESULTS

Between June 2001 and October 20, 2003, 42 patients were registered onto this study and randomized. Of those 42 patients, 19 patients were randomly assigned to chemotherapy alone, and 23 patients were assigned to chemotherapy with trastuzumab. Pretreatment characteristics of the patients in the two groups were similar and are listed in Table 1. The median age was slightly higher for the patients treated with chemotherapy plus trastuzumab. The distributions by the tumor T and N status were similar in the two groups, except for one patient who had T3b disease and was included in the chemotherapy plus trastuzumab arm. Two patients in the chemotherapy plus trastuzumab arm had synchronous bilateral breast cancers. Approximately half of the patients had hormone receptor–positive tumors. Most patients had HER2/*neu* status of tumors confirmed by FISH. For four patients, HER2 status was determined by immunohistochemistry only. One patient in each arm was subsequently found to be HER2 negative by FISH.

Table 1. Patient Characteristics

Characteristic	No. of Patients	
	P → FEC Alone (n = 19)	P → FEC + H (n = 23)
Age, years		
Median	48	52
Range	25-75	29-71
Tumor*		
T1	2	2
T2	13	15
T3	4	5
T4	0	1
Nodal status		
N0	7	10
N1	12	12
N2	0	1
Hormonal receptor status		
ER positive, PR positive	6	6
ER positive, PR negative	4	4
ER negative, PR positive	1	3
ER negative, PR negative	8	10
HER2 status		
FISH positive	17	19
IHC 3+ only	1	3
IHC 3+, FISH negative	1	1
Race		
White	13	13
African American	3	1
Asian	2	4
Hispanic	1	5

Abbreviations: P, paclitaxel; FEC, fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry.
*Two patients in the trastuzumab arm had synchronous bilateral disease.

Investigators were aware of the pathology results as each patient underwent the surgery phase of the trial. A high complete response rate was noted among early patients who completed surgical therapy. In October 2003, the DMC reviewed the study results. At the time that 42 patients had been registered onto the study, the pathology results were known for the first 34 patients. A formal interim analysis was not scheduled until the results for the first 82 patients were available, which was estimated to require at least 3 more years of accrual. Therefore, the DMC requested an extraordinary interim analysis based on Bayesian predictive probabilities and uniform prior distributions.[20,21] In particular, the DMC requested that they be presented with a calculation of the probability of eventually (ie, after the full sample size of 164 patients), showing statistical significance in pCR rates favoring the trastuzumab plus chemotherapy arm, based on the currently available information. This probability was 95%. The DMC found this to be compelling evidence that the study had reached its primary objective and recommended that accrual be suspended.

The pCR data for the first 34 patients, as reviewed by the DMC, and for all 42 patients randomized are listed in Table 2. Among the total patients, 26.3% of patients in the chemotherapy alone arm achieved pCR compared with 65.2% of the patients treated with trastuzumab plus chemotherapy. This difference was statistically significant ($P = .016$). The 95% CI for the 65.2% pCR rate observed on the trastuzumab plus chemotherapy arm ranged from 43% to 84%. An update of the Bayesian analysis incorporating results for 42 patients indicated a 96% probability that the trastuzumab plus chemotherapy arm would be found superior if accrual were continued to 164 patients. Of the patients who achieved pCR, one in the chemotherapy alone arm and five in the trastuzumab plus chemotherapy arm had residual ductal carcinoma-in-situ.

The pCR rate by hormone receptor status in the two arms was also evaluated. Patients with hormone receptor–positive and –negative disease had similar pCR rates compared with the overall population. Both ER-positive and ER-negative tumors treated with trastuzumab plus chemotherapy had higher pCR rates compared with the chemotherapy alone subgroups (Table 2). The extent of the residual disease in the breast (according to the largest one-dimensional measurement) and lymph node(s) is summarized in Table 2. For patients treated with trastuzumab plus chemotherapy, the size of residual tumors in the breast was significantly smaller compared with tumors of patients treated with chemotherapy alone. The difference in extent of residual disease in the lymph nodes, as measured by number of positive nodes, was not statistically significant. The median number of nodes evaluated histologically was similar between the two groups. Patients who had sentinel node biopsy had a median number of four nodes (range, four to five nodes) and three nodes (range, one to five nodes) in the chemotherapy alone arm (n = 7) and chemotherapy with trastuzumab arm (n = 9), respectively. Among patients who had axillary dissection, the median number of nodes was 16 (range, 12 to 26 nodes) and 16 (range, eight to 20 nodes) in the chemotherapy alone arm (n = 12) and chemotherapy with trastuzumab arm (n = 14), respectively. BCT was performed in 10 (52.6%) and 13 (56.5%) patients in the chemotherapy alone arm and chemotherapy with trastuzumab arm, respectively.

Clinical Response

The clinical response data are listed in Table 2. The clinical response was assessed by physical evaluation of the breast and nodes. Nine patients (47.4%) in the chemotherapy alone arm and 20 patients (86.9%) in the trastuzumab plus chemotherapy arm had clinical complete response. Most of the pCRs were observed in patients who had clinical complete responses. A small number of patients clinically judged to have partial response or no change in their disease status had pCR. Imaging studies included mammogram and ultrasound before surgery. In a number of patients who had pCRs, there were persistent abnormalities on imaging studies (Table 2). A number of patients with partial response on the paclitaxel phase of therapy achieved clinical complete response on the FEC phase of therapy. Response data are listed in Table 3 by each phase of therapy (paclitaxel and FEC).

Safety Data

The toxicity data are listed in Table 4. A higher fraction of patients treated with trastuzumab plus chemotherapy experienced grade 4 neutropenia during the paclitaxel phase of the therapy. A small number of patients had neutropenic fever, which required hospitalization for IV antibiotics. There were no treatment-related deaths. The chemotherapy dose was reduced because of neutropenia in five patients on the chemotherapy alone arm and 10 patients on the trastuzumab plus chemotherapy arm. Among the five patients in the chemotherapy arm who had dose reduction, one had a pCR. Ten patients had dose reduction because of neutropenia during the paclitaxel phase of therapy in the trastuzumab plus chemotherapy arm, and of those patients, eight had pCR. In the chemotherapy alone group, dose reduction was performed in one patient during the FEC phase of therapy. In the FEC phase of chemotherapy in the trastuzumab plus chemotherapy group, one patient had dose reduction because of neutropenia, and that patient had pCR. Three patients in each treatment arm had dose reduction for reasons other than myelotoxicity. A small number of patients experienced minor allergic reactions that did not require dose modifications. Patients were managed with additional appropriate premedications. In this small study, none of the patients developed clinical congestive heart failure (95% CI, 0% to 14.8%). With this number of patients, the probability of congestive heart

Table 2. Response by Treatment for All 42 Patients Except Where Noted

Response		No. of Patients: P → FEC Alone (n = 19)	No. of Patients: P → FEC + H (n = 23)	*P*
pCR				
Initial 34 patients				
%	25		66.7	.05
95% CI	7.3 to 52.4		41 to 87	
All 42 patients				
%	26.3		65.2	.016
95% CI	9.1 to 51.2		43 to 84	
pCR by hormonal receptor status, %				
Positive	27.2		61.5	
Negative	25		70	
Extent of residual disease by treatment				
Residual disease in breast				
None		5	15	.01
< 1 cm		3	5	
1-3 cm		9	1	
> 3 cm		2	2	
No. of positive nodes				
0		15	20	.25
1-3		2	3	
4-10		2	0	
> 10		0	0	
Physical evaluation				
Complete response				
Clinical response		9	21	
pCR		4	13	
Partial response				
Clinical response		9	1	
pCR		1	1	
Progressive disease				
Clinical response		1	0	
pCR		0	0	
Unknown				
Clinical response		0	1	
pCR		0	1	
Imaging studies, mammogram and ultrasound				
Complete response				
Imaging response		5	12	
pCR		4	7	
Partial response				
Imaging response		11	10	
pCR		1	7	
No change				
Imaging response		1	1	
pCR		0	1	
Progressive disease				
Imaging response		1	0	
pCR		0	0	
Unknown				
Imaging response		1	0	
pCR		0	0	

Abbreviations: P, paclitaxel; FEC, fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab; pCR, pathologic complete response.
*Reviewed by Data Monitoring Committee.

failure being 10% or higher is ruled out with a type II error rate of 8.9%. A greater than 10% decrease in the left ventricular ejection fraction was observed in five and seven patients in the chemotherapy alone and trastuzumab plus chemotherapy arms, respectively. Left ventricular ejection fraction returned to baseline values in those patients who had follow-up cardiac studies, except for one patient for whom the ejection fraction remains in the low normal

Table 3. Clinical Response by Phase of Therapy

P → FEC (No. of patients)		P → FEC + H (No. of patients)	
P	FEC	P	FEC
Physical evaluation			
CR 6	CR 5, PD 1	CR 14	CR 14
PR 11	CR 4, PR 7	PR 7	CR 6, PR 1
MR 1	PR 1	MR 1	Unknown 1*
NC 1	PR 1	NC 1	CR 1
Evaluation by ultrasound			
CR 2	CR 2	CR 4	CR 3, unknown 1*
PR 14	CR 3, PR 9, PD 1, unknown 1*	PR 18	CR 9, PR 9
MR 1	PR 1	MR 1	PR 1
NC 2	PR 1, NC 1	—	—

Abbreviations: P, paclitaxel; FEC, fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab; CR, complete response; PR, partial response; MR, minor response; NC, no change; PD, progressive disease.
*These patients did not have documentation of response after FEC.

range. Troponin T levels were evaluated at 3-week intervals during therapy. Values remained in the normal range for all patients, except for one patient on trastuzumab who had a single abnormal value.

Thus far, only one patient has developed recurrent disease, and that patient was on the chemotherapy alone arm. The median length of patient follow-up was 20 months (range, 8.8 to 36.6 months).

DISCUSSION

The objective of this prospective study was to determine the impact of the addition of trastuzumab on the pCR rate when patients with primary breast cancer were treated with sequential neoadjuvant paclitaxel and FEC chemotherapy. The pCR rate was 65% for patients treated with trastuzumab plus chemotherapy compared with 26% for patients treated with chemotherapy alone. For women treated with anthracycline-based neoadjuvant chemotherapy, pCR has been shown to predict improved disease-free and overall survival when compared with patients with less than pCR.[27-29] However, it remains to be determined whether increased pCR rate, as observed in this study with the sequential use of two chemotherapy regimens and limited exposure to trastuzumab, will result in improved disease-free and overall survival. A number of phase II studies have evaluated trastuzumab in the neoadjuvant setting with nondoxorubicin-containing chemotherapies.[30-34] In these studies, pCR rates have ranged from 19% to 35%. In this study, our objective was to achieve a 20% improvement in pCR rate with the addition of trastuzumab to chemotherapy. The results of this study demonstrated a higher pCR rate than anticipated. As a result, the study was modified, and the control arm was stopped at the recommendation of the DMC. In the revised, ongoing study, all patients with HER2-positive disease are being offered chemotherapy plus trastuzumab. With additional patients, the CI of the pCR rate will be narrowed, and follow-up of all patients will provide additional safety data.

Despite the high pCR rate, BCT was performed in only approximately half of the patients. This may be a reflection of a number of factors that include persistent abnormalities on imaging studies and patient preferences. Better imaging modalities or cancer markers are needed that provide accurate information regarding persistent (or lack thereof) invasive disease. With this approach, a larger fraction of patients with no invasive cancer, if accurately identified before local therapy, may be candidates for breast preservation.

Table 4. Adverse Events

Event	No. of Patients	
	P → FEC Alone (n = 19)	P → FEC + H (n = 23)
Grade 4 neutropenia*	11	21
Neutropenic fever	8	8
Neutropenic infections	3	5
Hospitalization	1	3
Nonneutropenic infections	4	7
Chemotherapy dose reduction as a result of neutropenia	5	10
Allergic reactions, no therapy modification	4	4
Cardiac safety data		
CHF	0	0
> 10% decrease in ejection fraction	5	7
Decrease on P	0	4
Decrease on FEC	5	3
Improvement in ejection fraction on follow-up evaluation	2	3
Abnormal troponin-T	0	1

Abbreviations: P, paclitaxel; FEC, fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab; CHF, congestive heart failure.
*$P = .03$.

Cardiac toxicity has been an ongoing concern related to the use of trastuzumab in early-stage breast cancer. In this study, trastuzumab was administered concurrently with paclitaxel- and epirubicin-based chemotherapy. Since the publication of the pivotal trial in metastatic, HER2-overexpressing breast cancer, it has been known that the simultaneous combination of doxorubicin and trastuzumab resulted in a high rate of clinical and subclinical cardiotoxicity, but data from large multicenter trials have not resulted in toxicity rates sufficiently high to curtail enrollment.[35] On the basis of those results, subsequent studies, especially those performed in the adjuvant or neoadjuvant setting, have avoided the simultaneous administration of anthracyclines and trastuzumab. However, retrospective analyses of the correlation of HER2 overexpression and chemotherapy response have suggested that anthracyclines had an important role in the management of HER2-overexpressing breast cancer.[9,36-42] Therefore, we reasoned that the simultaneous combination of trastuzumab with an anthracycline could be advantageous, as long as cardiac toxicity could be prevented or minimized.

There are ongoing studies of combinations that include trastuzumab with epirubicin or doxorubicin HCl liposome injection, two anthracyclines with reported lower cardiac toxicity effects than doxorubicin.[43-47] These preliminary safety data and the intent to limit cumulative dose of the anthracycline in the sequential combination with a taxane suggested that the combination with trastuzumab could be administered safely, without excessive cardiac toxicity. Epirubicin, the anthracycline included in the combination in this study, has been reported to have a better cardiac safety margin. There is no evidence of steep dose-dependent response with doxorubicin beyond 50 to 60 mg/m^2 in the adjuvant setting. However, for epirubicin, there is a dose-dependent response in the adjuvant setting. Administration of FEC100, using epirubicin 100 mg/m^2 per cycle, results in significantly improved 10-year survival compared with FEC50, using epirubicin 50 mg/m^2.[48] We selected 75 mg/m^2 as a safe compromise between efficacy and cardiac safety because concurrent trastuzumab was planned. Four cycles of epirubicin at this dose would result in a cumulative dose of 300 mg/m^2, which is approximately one third of the cardiotoxic threshold of epirubicin. With this approach, we expected to reduce the risk of cardiac dysfunction. In this study, the duration of trastuzumab was also limited to 24 weeks. The limited exposure of epirubicin concomitantly with trastuzumab has not resulted in any clinical cardiac dysfunction. A small number of patients did show a transient drop in the cardiac ejection fraction; however, cardiac ejection fractions returned to original normal levels on follow-up evaluation.

In this study, pCR rates were high both in patients with hormone receptor–positive and hormone receptor–negative disease. This was in contrast to our earlier experience in patients unselected by HER2 status treated with neoadjuvant therapy. In a retrospective review of more than 1,000 patients with primary breast cancer, pCRs in studies with anthracycline-based chemotherapies ranged from 2% to 14% (mean, 5%) in patients with hormone receptor–positive disease compared with 7% to 55% (mean, 21%) in patients with hormone receptor–negative disease.[49] In that analysis, the HER2 status of the tumors was not known. Unlike our previous experience with preoperative chemotherapy, pCR rates in this study were similar for ER-positive and ER-negative tumors. HER2 status seems to be of more influence in pCR outcome. Further clinical and laboratory evaluation of this interaction of ER and HER2 and response to chemotherapy is warranted. Additional follow-up of these patients and continued accrual on the ongoing trial will provide additional efficacy and safety data for this treatment approach.

These results represent the highest reported pCR rate in this patient population. The most logical explanation for this high pCR rate is the use of two potentially non–cross-resistant chemotherapies administered sequentially in combination with trastuzumab. Other possibilities include longer duration of neoadjuvant therapy compared with earlier studies. Additional studies are needed to define the pCR rate with a narrow CI and establish the cardiac risk of this combination. Follow-up of our study patients will provide data that will establish whether pCR rate will translate into high disease-free and overall survival rates as observed in other neoadjuvant studies. If the long-term follow-up confirms prolonged overall survival and low or modest incidence of cardiac toxicity, this combination may have a favorable risk to benefit ratio for patients with HER2-positive breast cancer.

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The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Employment: Michael S. Ewer, Pfizer. Honoraria: Aman U. Buzdar, Pfizer; Debra K. Fyre, Pfizer, Pharmacia; Aysegul A. Sahin, Genentech; Michael S. Ewer, Alza. Research Funding: Aman U. Buzdar, Bristol-Myers Squibb, Genentech, Pfizer; Banu K. Arun, AstraZeneca, NCI, Pfizer. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and Disclosures of Potential Conflicts of Interest found in Information for Contributors in the front of each issue.

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