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Predictors of Response to Preoperative Chemotherapy in Her2-positive Breast Cancer Patients

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Predictors of Response to Preoperative Chemotherapy in Her2-positive Breast Cancer Patients

By

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M.D., Emory University School of Medicine, 2001

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An abstract of
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Master of Science
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ABSTRACT

Predictors of Response to Preoperative Chemotherapy in Her2-positive Breast Cancer Patients

By Amelia B. Zelnak

Objective. The aim of this study was to determine the pathologic complete response rate (pCR) to preoperative, trastuzumab-based chemotherapy in Her2-positive, early-stage breast cancer patients and to determine predictors of pCR.

Methods. This is a retrospective study of 27 women with early-stage, Her2-positive breast cancer who received preoperative, trastuzumab-based chemotherapy. Analysis of predictor variables was performed using multivariate logistic regression.

Findings. A total of 27 patients were included in this analysis. The overall pCR rate among early-stage Her2-positive breast cancer patients receiving trastuzmab-based preoperative chemotherapy was 66.7%. The pCR rate among patients treated as part of phase II clinical trial was 63.6%. In univariate analysis, no statistically significant association was seen between the following predictor variables and pCR: tumor size, estrogen receptor (ER) status, anthracycline-based chemotherapy, high nuclear grade, age, clinical nodal status, and body mass index. In multivariate analysis, no association was seen between the predictor variables and pCR.

Conclusions. This study did not identify any variables that predicted having a pathologic complete response to preoperative chemotherapy among Her2-positive patients. The pCR rate was higher than previously seen in clinical trials, and implies that the most significant predictor of pCR to preoperative trastuzumab-based chemotherapy is being Her2-positive.

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INTRODUCTION

Breast cancer affects 1 in 7 women, 80% of whom present with early stage disease. Induction or neoadjuvant therapy was initially developed in the hopes that survival could be improved by administering chemotherapy early in the course of disease when metastatic disease is microscopic. This was found not to be the case and survival was noted to be the same regardless of whether chemotherapy is given before or after surgery (1). However, induction chemotherapy can shrink breast tumor size, making more tumors amenable to breast-conserving treatments. Additionally, unlike adjuvant or post-operative chemotherapy, induction chemotherapy allows an assessment of markers of *in vivo* chemosensitivity.

Approximately 20-30% of all breast cancers overexpress Her2, a member of the epidermal growth factor receptor family of tyrosine kinase receptors. Overexpression of Her2 has been associated with increased rates of recurrence and overall worse prognosis. The addition of trastuzumab to adjuvant chemotherapy has resulted in highly significant reductions in recurrence and improvement in overall survival. However, the optimal combination of trastuzumab with neoadjuvant chemotherapy has not been well-characterized. Pathologic complete response (pCR) at the time of surgery is often used as a surrogate endpoint for disease-free survival based upon correlations seen in prior studies of preoperative chemotherapy. This endpoint is determined at the time of surgery and is useful in assessing novel combinations in earlier phase clinical trials.

We have been conducting a single-arm phase II clinical trial investigating the combination of trastuzumab with nab-paclitaxel (Abraxane™; Abraxis Bioscience, Inc., Los Angeles), albumin-bound paclitaxel followed by the combination of trastuzumab with vinorelbine. The primary endpoint of the study was to determine the pCR rate to this preoperative chemotherapy regimen. The study has a planned accrual of 50 patients. The pCR rate from this trial will be compared to historical control pCR rate of 26% from National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 clinical trial (2). To date, 21 subjects have

enrolled on the study, 11 of whom have completed preoperative chemotherapy and undergone surgical resection.

In order to examine predictors of pCR in this patient population, the data from the 11 patients on this trial were combined with 16 additional early-stage Her2-positive breast cancer patients who received preoperative, trastuzumab-based chemotherapy. These patients were identified from a clinical database of 373 breast cancer patients treated in Department of Hematology and Oncology at the Emory Winship Cancer Institute from 2005 to 2008.

BACKGROUND

There have been multiple large clinical trials investigating the efficacy of preoperative chemotherapy. The NSABP B-18 trial randomized 1523 patients with resectable breast cancers to adriamycin and cyclophosphamide (AC) for 4 cycles before or after surgery. At 9 years, there was no significant difference between the 2 arms of the trial in disease-free or overall survival (DFS or OS) (1,2). Breast tumor size decreased in 80% of patients randomized to the pre-operative arm, and there was no invasive cancer in the breast at the time of surgery (pathologic complete response (pCR)) in 13% of patients. Response of individual breast tumors to pre-operative therapy did correlate with survival. The greatest advantage was noted in patients who achieved a pCR (correlation between OS at P=0.009 & DFS at P= 0.004). Furthermore, patients who obtained a clinical complete response were three times more likely to demonstrate a pathological complete response than were those only achieving a partial clinical response.

Subsequently, the NSABP B-27 trial randomized patients with resectable breast tumors to one of 3 arms: pre-operative AC for 4 cycles, pre-operative AC for 4 cycles followed by docetaxel (100mg/m^2) for 4 cycles and pre-operative AC for 4 cycles followed by surgery and then 4 cycles of docetaxel (3,4). The addition of docetaxel after AC resulted in an increased complete clinical response (65% vs. 40% P=<0.001), increased complete pathological response (25.6% vs. 13.7% P=<0.001) and a decreased rate of axillary nodal positivity (40.5% vs. 48.5% P=0.01). There was a trend towards improved DFS with the addition of docetaxel, however a significant improvement in OS was not observed. Analysis of patients who achieved a pCR did reveal that this subgroup of patients had a statistically improved DFS and OS (2).

These studies included all breast cancer subtypes regardless of hormone receptor status, and they were conducted prior to the adoption of trastuzumab –based chemotherapy as standard of care for Her2-overexpressing, early-stage breast cancer patients. Trastuzumab (Herceptin®; Genentech, Inc., South San Francisco, CA) is a recombinant, monoclonal antibody targeted

against HER2. Her2 is a member of the epidermal growth factor receptor family of tyrosine kinase receptors, and is normally involved in regulation of cell growth. Overexpression of HER2 is associated with increased risk of recurrence and overall worse prognosis (5). Approximately 20-30 % of all breast cancers are Her2-positive. Trastuzumab combined with chemotherapy improves the outcome of patients with HER2 overexpressing metastatic breast cancer and has become the standard of care for the treatment of these patients (6).

Based upon the improved outcome in the metastatic setting for the addition of trastuzumab to chemotherapy, several large studies were performed in the earlier stage setting to determine if long-term outcome could also be improved for these breast cancer patients. Joint analysis of two phase III clinical trials (NSABP-B31 and NCCTG-N9831) compared chemotherapy with and without trastuzumab in the adjuvant treatment of HER2 overexpressing breast cancer, and demonstrated highly significant reductions in recurrence and improvement in overall survival. Patients treated with AC followed by paclitaxel plus trastuzumab had a 4-year DFS or 85%, compared to 67% for those treated with chemotherapy alone (7).

The Breast Cancer International Research Group (BCIRG) conducted a similar large adjuvant trial of trastuzumab-based chemotherapy; however this study included a novel, non-anthracycline based regimen (docetaxel, carboplatin, and trastuzumab). The main toxicity associated with the addition of trastuzumab to chemotherapy has been an increase in cardiac toxicity. The rates of symptomatic heart failure in NSABP B31 and NCCTG N9831 were 3.8% and 3.3% respectively, whereas the rate of symptomatic heart failure on the non-anthracycline containing arm of BCIRG006 was 0.4% (8-11). Updated analysis of the BCIRG 006 study demonstrated that the addition of trastuzumab to chemotherapy resulted in a significant improvement in outcome. Additionally, there was no statistically significant difference between the anthracycline-containing and non-anthracycline-containing regimen. Based upon these results both AC followed by paclitaxel and trastuzumab and docetaxel, carboplatin, and trastuzumab

have been accepted as standard adjuvant chemotherapy regimens for early-stage Her2-positive breast cancer.

Trastuzumab has been shown to significantly increase pCR when combined with chemotherapy in patients with HER2-positive breast cancers. Buzdar et al randomized 42 patients to paclitaxel followed by FEC (5-fluorouracil, epirubicin and cytoxan), with and without trastuzumab (12,13). The pCR rate was 67% in patients treated with trastuzumab, compared to 25% in patients in the control group. The trial was closed after this initial analysis because of the significantly higher rate of pCR in the trastuzumab-treated patients. Gianni et al have reported preliminary results of another study in which locally advanced Her2-positive breast cancer patients received 3 cycles of adriamycin and cyclophosphamide followed by 4 cycles of paclitaxel, followed by 3 cycles of CMF (cyclophosphamide, methotrexate, with or without trastuzumab. The addition of trastuzumab significantly increased the pCR rate (43% vs 23%, p=0.002) (14).

As expected, the addition of trastuzumab to preoperative chemotherapy has resulted in improved pCR rates which have often been used as a surrogate endpoint for disease-free survival. However, the optimal combination of trastuzumab with chemotherapeutic agents in neoadjuvant treatment of HER2 overexpressing breast cancer has not been fully characterized. Additionally, the increased cardiac toxicity associated with the combination of trastuzumab and anthracyclines has prompted additional investigation into non-anthracycline-based regimens. Currently, chemotherapy regimens used in the adjuvant setting are used in the neoadjuvant setting. In this study, we examined the pCR rate as well as determined if there were factors that could predict which patients would achieve a pCR. If predictive factors were identified, this would have implications in determining which patients were good candidates for preoperative therapy.

METHODS

H_0: There is no association in predictor variables between Her2-positive breast cancer patients receiving preoperative chemotherapy who achieve a pCR compared to those who do not achieve a pCR.

Study Design: This was a retrospective study of Her2-positive breast cancer patients who received preoperative, trastuzumab-based chemotherapy. The clinical database of the Emory Winship Cancer Institute breast medical oncology program was used to identify patients with stage I to III Her2-positive breast cancer who received trastuzumab-based preoperative chemotherapy from 2005 to present. 373 patients were in the database at time of analysis, 54 of whom were Her2-positive. Of these patients, 16 received preoperative chemotherapy. These patients were not treated as part of a clinical trial, and received chemotherapy regimens that are standard of care in the adjuvant setting: either 4 cycles of doxorubicin and cyclophosphamide followed by 12 weeks of weekly paclitaxel and trastuzumab or 6 cycles of docetaxel, carboplatin, and trastuzumab.[19] Patient information, tumor characteristics, and outcome of preoperative chemotherapy at time of surgery were available for these 16 patients. Data from an additional 11 subjects who were treated as part of a phase II clinical trial of trastuzumab-based chemotherapy were also included in analysis. Subjects treated as part of the phase II trial received 4 cycles of dose dense nab-paclitaxel (260 mg/m^2) every 2 weeks followed by weekly vinorelbine for 12 weeks (25 mg/m^2) in combination with trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly). Following completion of preoperative chemotherapy, patients then underwent surgical resection at which time the outcome of pCR was determined.

Patients: Inclusion criteria were pathologically confirmed diagnosis of Her2-positive early stage breast cancer, received preoperative trastuzumab-based chemotherapy, and underwent surgical

resection after completion of chemotherapy. Patients were excluded if they had metastatic disease outside the breast and ipsilateral lymph nodes at the time of diagnosis.

Predictor variables: Predictor variables were tumor size, estrogen receptor (ER) status, anthracycline-based chemotherapy, high nuclear grade, age, clinical nodal status, menopausal status, and body mass index. Data was obtained from the breast oncology database, the medical record, and from documentation collected as part of phase II clinical trial.

Outcome variable: The outcome variable for the multivariate analysis was pathologic complete response (pCR) at time of surgical resection, defined as the absence of invasive cancer in surgical specimen, allowing for residual ductal carcinoma in situ.

Sample Size: Overall, 27 patients were identified who received preoperative, trastuzumab-based chemotherapy. Patients were treated at the Emory Winship Cancer Institute, Grady Cancer Center of Excellence, and at community sites as part of Georgia Center for Oncology Research and Education (GA-CORE).

Analysis: This study was analyzed as a case-control study with the odds ratio as a measure of effect showing the relative odds of exposure. Analyses were performed using SAS v 9.2. The outcome variable for the univariate and multivariate logistic regression was pCR. Fisher's exact test was used to determine if there was a statistical association between the baseline characteristics and group assignment. Multivariate logistic regression was used to determine which variables were predictive of pCR at the time of surgery. Co-linearity was evaluated and adjusted for in the final model.

RESULTS

Baseline Patient Characteristics (Table 1): A total of 27 patients with Her2-positive, early-stage breast cancer who received preoperative trastuzumab based chemotherapy were included in this analysis. The median age of the population was 48 years of age. The median tumor size at presentation was 3.65 cm. 22% of the patients had breast tumors under 2 cm in size (T1 tumor); 56% had tumors between 2 and 5 cm (T2 tumor); 11% had a tumor over5 cm (T3 tumor); and 11% had overlying skin retraction (T4 tumor). 56% of subjects included were clinically node positive prior to receiving preoperative chemotherapy. 44% of patients had high grade tumors. 63% were estrogen and progesterone receptor (ER/PR) negative. Mean body mass index was 27.1. 67% of the patients were premenopausal prior to receiving chemotherapy. 66% of the patients were Caucasian and 26% were African American.

Pathologic Complete Response (pCR) Rates (Table 2): The overall pCR rate for the study population was 66.7%. Among the eleven patients treated as part of the phase II clinical trial, the pCR rate was 63.6%. Among the patients treated off-protocol with standard of care chemotherapy regimens, the pCR rate was 68.8%. There were no differences seen in frequency of predictor variables among patients who achieved a pCR and those who did not achieve a pCR (Table 3).

Analysis of predictor variables and their association with having a pathologic complete response (Table 4): On univariate analysis, tumor size, estrogen receptor (ER) status, anthracycline-based chemotherapy, high nuclear grade, age, clinical nodal status, menopausal status and body mass index were not associated with having a pCR after preoperative chemotherapy.

Evaluation of predictive factors for pCR among Her2-positive breast cancer patients receiving preoperative chemotherapy: On multivariate analysis, none of the predictive factors included

were associated with achieving a pCR (Table 5). No interaction was seen among the variables included in the model. A significant correlation was seen between age and menopausal status and age and estrogen receptor status (Table 6). The multivariate analysis was repeated without age included as a predictor variable, however none of the other predictor variables were associated with pCR (Table 7).

DISCUSSION

The data collected through the Emory Breast Oncology Database affords an opportunity to determine if baseline patient and tumor characteristics predict for a favorable response to preoperative chemotherapy, namely, pathologic complete response at the time of surgery. Predicting which patients are likely to respond to treatment could potentially impact treatment recommendations for future patients who are deciding whether to receive preoperative chemotherapy versus to proceed directly to surgery. Overall, the rate of pCR in the population studied was higher than anticipated based upon previous results from clinical trials of Her2-positive breast cancer patients.

We were not able to identify any predictive factors for achieving a pCR among the 8 predictor variables studied. Due to the high rate of pCR, the most significant predictor of achieving a pCR in this patient population was being Her2-positive. In addition, a number of the patients who did not achieve a pCR had a complete clinical response and had minimal residual disease present at the time of surgery. In the future, one could use residual cancer burden as outcome variable, comparing patients who achieve a pCR or have minimal residual disease to those with a moderate or significant amount of residual disease, to further assess factors predictive of pCR.

The major limitation of this study was the small number of patients included, however based upon the point estimates and wide confidence intervals, one would likely need a very large patient population to identify any associations between predictor variables and outcome. We did perform repeat analysis of the data with fewer predictor variables included; however, none of the remaining predictor variables, tumor size, nodal status, estrogen receptor status, and anthracycline use was associated with the outcome pCR.

In conclusion, this study was not able to identify predictors of pCR among Her2-positive patients receiving preoperative chemotherapy. The most important predictor of pCR is likely being Her2-positive. Based upon the overall high pCR rate seen in this patient population, patients should be considered excellent candidates for preoperative chemotherapy in order to improve their likelihood of undergoing breast-conserving surgery.

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TABLES

Table 1. Baseline Characteristics of Patients

	No. pts (%) (n=27)
Median age	48
Median tumor size	3.65 cm
Clinical Tumor Stage	
T1	6 (22.2%)
T2	15 (55.6%)
T3	3 (11.1%)
T4	3 (11.1%)
Clinical Nodes	
Negative	12 (44.4%)
Positive	15 (55.6%)
Nuclear Grade	
Low/medium	15 (55.6%)
High	12 (44.4%)
ER Status	
Positive	10 (37%)
Negative	17 (63%)
PR Status	
Positive	10 (37%)
Negative	17 (63%)
Body Mass Index	27.1
Menopausal Status	
Premenopausal	18 (66.7%)
Postmenopausal	9 (33.3%)
Race	
Caucasian	18 (66.7%)
African American	7 (25.9%)
Other	2 (7.4%)

Table 2. Pathologic complete response (pCR) rates

	Overall Population (n=27)	Preoperative Trial (n=11)
pCR	18/27 (69.2%)	7/11 (63.6%)

Table 3. Frequency of predictor variables in patients who achieved pathologic complete response (pCR) versus those who did not achieve pCR

Characteristic	pCR (n=18)	no pCR (n=9)	p value[d]
cT3-T4[a]	22.2%	22.2%	1.00
ER-positive	33.3%	44.4%	0.68
Anthracycline	50.0%	33.3%	0.68
High Nuclear Grade	44.4%	44.4%	1.00
Postmenopausal	33.0%	33.3%	1.00
Age[b]	50.0%	33.3%	0.68
Clinical Node-positive	55.6%	55.6%	1.00
Body Mass Index (BMI)[c]	33.3%	22.2%	0.67

a cT3-4 as compared with cT1-2
b above median age as compared with below median age
c above median BMI as compared with below median BMI
d 2-sided Fisher exact used

Table 4. Predictive factors of pathologic complete response in univariate analysis

	OR (95% CI)
Tumor Size[a]	0.80 (0.50 – 1.29)
ER-positive	0.50 (0.047 – 5.35)
Anthracycline	3.52 (0.34 – 36.70)
High Nuclear Grade	0.77 (0.12 – 4.96)
Postmenopausal	2.81 (0.092 – 85.42)
Age[b]	0.94 (0.78 – 1.14)
Node-positive	0.64 (0.091 – 4.46)
Body Mass Index (BMI)[c]	1.16 (0.94 – 1.43)

[abc] Modeled as continuous variables

Hosmer and Lemeshow Goodness of Fit Test: $\chi^2 = 8.29$, p=

c above median BMI as compared with below median BMI

Table 5. Predictive factors of pathologic complete response in multivariate logistic regression analysis

Characteristic	Multivariate analysis OR (95% CI)
Tumor Size[a]	0.80 (0.50 - 1.29)
ER-positive	0.50 (0.047 - 5.35)
Anthracycline	3.52 (0.34 - 36.70)
High Nuclear Grade	0.77 (0.12 - 4.96)
Postmenopausal	2.81 (0.092 - 85.42)
Age[b]	0.94 (0.78 - 1.14)
Node-positive	0.64 (0.091 - 4.46)
Body Mass Index (BMI)[c]	1.16 (0.94 - 1.43)

[abc] Modeled as continuous variables

Hosmer and Lemeshow Goodness of Fit Test: $\chi^2 = 8.29$, p=0.31

Table 6. Significant Correlation Between Age and Menopausal Status, and Age and ER Status

Predictors	*r*	p value
Age and Menopausal status	0.82	<0.0001
Age and ER status	-0.44	0.02

r = Pearson Correlation Coefficient

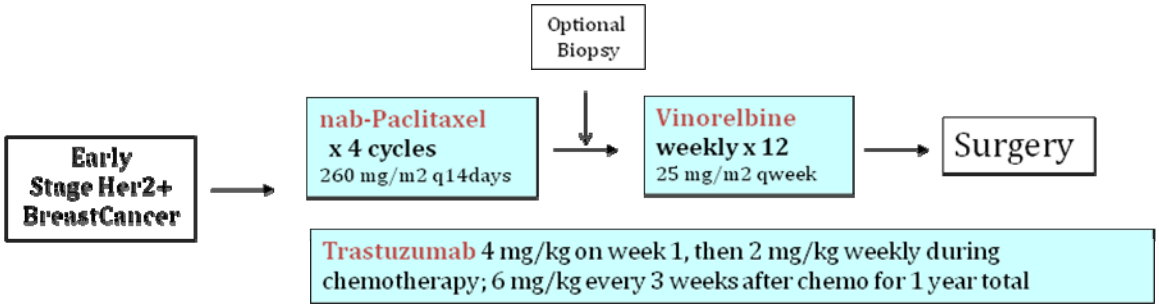
Table 7. Predictive Factor Analysis for pathologic complete response for the Multivariate Model excluding Age due to Collinearity with ER Status and Menopausal Status

Characteristic	Multivariate analysis OR (95% CI)
Tumor Size[a]	0.81 (0.50 - 1.31)
ER-positive	0.60 (0.063 - 5.68)
Anthracycline	4.47 (0.47 - 42.7)
High Nuclear Grade	0.70 (0.11 - 4.37)
Postmenopausal	1.21 (0.14 - 10.22)
Node-positive	0.64 (0.091 - 4.46)
Body Mass Index (BMI)[b]	1.16 (0.94 - 1.43)

ab Modeled as continuous variables

Hosmer and Lemeshow Goodness of Fit Test: $\chi^2 = 9.14$, p=0.24

Appendix 1. Study schema for phase II preoperative clinical trial of nab-paclitaxel and trastuzumab followed by vinorelbine and trastuzumab.



Appendix 2. Inclusion and Exclusion Criteria for phase II preoperative trial.

Inclusion Criteria	Exclusion Criteria
• Histologically confirmed Her2-positive breast cancer (3+ Her2 overexpression by IHC or 2+ by IHC and FISH amplification) • Stage I, II, or IIIA (T1c – T3, N0-N2) • No evidence of disease outside breast and ipsilateral axillary nodes • Measurable disease by either breast imaging or physical exam • ECOG performance status of 0 to 1 • Adequate hematopoietic, hepatic, renal function • LV ejection fraction greater than 50%	• Pregnant or lactating women • Prior chemotherapy, hormonal therapy, biologic therapy or radiation therapy for breast cancer • Evidence of peripheral neuropathy > grade 1 • History of previous malignancy other than carcinoma in situ of cervix or basal/squamous cell carcinoma of skin

Appendix 3. Baseline patient characteristics for patients enrolled on phase II clinical trial.

	Breast Cancer Database (n=16)
Median age	46.2 years
Median tumor size	3.6 cm
Clinical Tumor Stage	
T1	5 (31.3%)
T2	7 (43.7%)
T3	2 (12.5%)
T4	2 (12.5%)
Clinical Nodes	
Negative	7 (43.7%)
Positive	9 (56.3%)
Nuclear Grade	
Low/medium	7 (43.7%)
High	9 (56.3%)
ER Status	
Positive	7 (43.7%)
Negative	9 (56.3%)
PR Status	
Positive	7 (43.7%)
Negative	9 (56.3%)
Body Mass Index	25.7
Menopausal Status	
Premenopausal	12 (75%)
Postmenopausal	4 (25%)
Race	
Caucasian	11 (68.7%)
African American	3 (18.8%)
Other	2 (12.5%)