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Predictors of pathological complete response to neoadjuvant chemotherapy in stage II and III breast cancer: The impact of chemotherapeutic regimen

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Abstract. In this study, we sought to determine the predictors of pathological complete response (pCR) and compare the chemotherapeutic regimens administered to breast cancer patients with and those without pCR. We retrospectively reviewed the data of 879 patients treated at the Alvin J. Siteman Cancer Center between 2006 and 2010, to identify patients who were diagnosed with primary stage II or III breast cancer and received neoadjuvant chemotherapy. Patients who received only neoadjuvant endocrine therapy were considered to be ineligible. Patient, tumor, and treatment characteristics, including type of chemotherapy, were compared between patients who did and those who did not achieve pCR using Chi-square or Fisher's exact tests and multivariate logistic regression analysis. Two-sided P-values of <0.05 were considered significant. Of the 333 patients who met the inclusion criteria, 61 (18.3%) had documented pCR. Compared with patients not achieving pCR, a greater proportion of patients with pCR had stage II disease (80.3 vs. 68%, P=0.057), had poorly differentiated (grade 3) tumors (82 vs. 59.2%, P<0.001), had negative lymph node involvement (41 vs. 34%, P=0.0004) and had tumors that were HER2-amplified (41 vs. 23.5%, P=0.0054). A greater proportion of patients with pCR received taxane-based chemotherapy (23 vs. 12.5%, P=0.016) or trastuzumab in conjunction with chemotherapy (41.0 vs. 16.9%, P<0.001). No patients receiving solely anthracycline-based therapy achieved pCR in our study. Our study demonstrated that, for stage II and III breast cancer, lower stage, negative lymph node involvement and HER2 receptor amplification were each associated with pCR. Taxane therapy and the concurrent use of trastuzumab were also associated with a higher likelihood of pCR.

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Introduction

Neoadjuvant chemotherapy for the treatment of breast cancer has undergone significant evolution over time. Historically, neoadjuvant chemotherapy was used only for tumors considered inoperable at presentation. However, this changed after the publication of the well-known National Surgical Adjuvant Breast and Bowel Project study results, which demonstrated that neoadjuvant chemotherapy, in comparison to adjuvant, was not associated with significant differences in disease-free or overall survival and was associated with higher rates of breast-conserving surgery (1,2). Neoadjuvant chemotherapy use was subsequently broadened to include large, operable tumors with the aim of achieving breast conservation.

In addition to breast conservation, neoadjuvant chemotherapy allows for an *in vivo* assessment of response to therapy, while also providing early treatment of the primary tumor and potential micrometastatic disease (3). Pathological complete response (pCR), often used as a surrogate endpoint to assess the efficacy of neoadjuvant chemotherapy, is also considered to be a strong prognostic measure of long-term clinical outcomes, including disease-free and overall survival (4-6). Hence, identifying and validating factors which predict pCR or improve pCR rates are crucial in breast cancer management.

Furthermore, anthracyclines have been considered traditionally as the most standard and active among breast cancer chemotherapy drugs. In an effort to improve pCR rates, other studies investigated the impact of combining different chemotherapeutic agents in the neoadjuvant setting (7-10). In our study, we not only sought to identify pCR rates and predictors at a single institution, but also to examine the administered chemotherapeutic regimens, and compare and contrast the regimens between patients who did and those who did not achieve pCR.

Patients and methods

Patient selection. During a retrospective review of 879 patients who were treated for a first primary breast cancer at the Alvin J. Siteman Cancer Center between January, 2006 and December, 2010, we identified patients who received neoadjuvant chemotherapy for pathologically confirmed invasive (stage II and III) breast cancer. We restricted our analysis to

stage II and III disease in the specified 5-year period in order to evaluate a more homogeneous population of patients receiving neoadjuvant chemotherapy, with or without other neoadjuvant treatment, as neoadjuvant treatment decisions were likely made based on similar overarching guidelines during this period (based on tumor size and grade, presence or absence of lymph node metastases, receptor status and recommended chemotherapeutic regimens). The medical records of patients who received neoadjuvant chemotherapy were reviewed, to determine which of these patients' tumors exhibited a pCR, defined as no evidence of residual invasive malignancy in the breast or axilla. As ductal carcinoma *in situ* (DCIS) generally does not regress with chemotherapy and evidence of its impact on prognosis is equivocal (11,12), patients with only residual DCIS following neoadjuvant systemic therapy were included in the pCR cohort. Patients who received only neoadjuvant endocrine therapy without mention of chemotherapy in the neoadjuvant setting were deemed ineligible for inclusion, mainly to avoid including patients who rarely achieve pCR, as previous studies have demonstrated that, while a large number of patients undergoing neoadjuvant endocrine therapy display some evidence of clinical response, pCR is infrequent (13-16). Additionally, we determined the specific neoadjuvant systemic therapy received by each of the identified patients to assess the potential impact of the chemotherapeutic regimen received on the pCR rates observed. The regimen administered to each patient was selected at the discretion of the medical oncologist, based on established standards or clinical trials in place at the time of therapy.

This study was initiated after Institutional Review Board approval was obtained, with a waiver of consent given the retrospective nature of the study.

Statistical analysis. We used the Wilcoxon rank-sum tests (for continuous variables), Chi-square or Fisher's exact tests (for categorical variables) and unadjusted logistic regression to examine clinical characteristics potentially associated with pCR, including age, race, lymph node involvement, histology, TNM stage, tumor grade, estrogen receptor (ER) and progesterone receptor (PR) status, and presence of HER2 amplification. Tumor size was not examined as a discrete variable, but rather as a component of stage. Biomarker/receptor status, stage and factors significant at P<0.2 in unadjusted tests were included as independent variables in multivariate logistic regression models that were further refined using backwards elimination.

Two regression models for the outcome pCR as a yes/no binary measure were created, one featuring each individual receptor status (i.e., PR, HER2) and the other using a composite biomarker status reported of hormone receptor status plus/minus HER2 amplification. A hormone receptor-positive (HR+) cancer was defined as an ER-positive and/or PR-positive cancer, whereas a hormone receptor-negative (HR-) cancer was defined as an ER-negative and/or PR-negative cancer. These definitions led to the generation of four categories for comparison in the composite biomarker analysis as follows: HR+/HER2-, HR+/HER2+, HR-/HER2- and HR-/HER2+. Additionally, grade was analyzed by combining well- and moderately differentiated cancers (grade 1 and 2) and comparing them to poorly differentiated cancers (grade 3). We report adjusted odds ratios (ORs) and 95% confidence intervals (CIs) significant at two-tailed P<0.05. The statistical analyses were conducted using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA).

Results

pCR rates and predictors. Over the 5-year period reviewed, 333 patients received neoadjuvant chemotherapy. Among these patients, the majority had stage II disease (70.3%) and tumors that were ER+ (52.3%), PR- (55.9%), HER2-non-amplified (HER2-; 73.3%), poorly differentiated (i.e., grade 3; 63.4%), and a ductal histology (77.5%). A total of 61 patients (18.3%) had pCR. Descriptive statistics of the study sample grouped by pCR status are shown in Table I.

In unadjusted tests, pCR was associated with higher tumor grade (P=0.0035), no lymph node involvement (P=0.0013), HER2 amplification (P=0.0061), ER-negative (P=0.027) and PR-negative status (P<0.001). Also observed was an inverse association between pCR and HR+/HER2- status (P<0.001). These results are shown in Table II.

The results of separate multivariate logistic regression models, one featuring individual biomarkers and the other including composite biomarkers, are also reported in Table II. In the model featuring individual biomarkers, HER2 amplification (P=0.0095), PR-negative status (P=0.0081) and absence of lymph node involvement (P=0.0039) predicted a higher likelihood of pCR. In the multivariate model including the composite biomarkers, the HR+/HER2- subtype and any lymph node involvement (P=0.0049) resulted in a lower likelihood of pCR.

Neoadjuvant systemic therapy. Of the 333 patients in the study sample, complete records of the administered chemotherapeutic regimens were available for 323 (97%); 252 patients received a combined regimen of anthracyclines and taxanes, 48 received a taxane-only regimen, 19 received an anthracycline-only regimen and 4 received a platinum agent-based regimen. Following completion of all the cycles of neoadjuvant chemotherapy, 46/252 patients receiving combined regimen of anthracyclines and taxanes, 14/48 patients in the taxane-only subgroup, 1/4 patients receiving platinum agent-based therapy and none of the patients (0/19) in the anthracycline-only subgroup exhibited pCR (P=0.016). Furthermore, administration of neoadjuvant therapy with or without trastuzumab was recorded for 329 (98.8%) patients; 71 patients (21.3%) received trastuzumab, either concomitant with or sequential to chemotherapy, while 258 patients did not receive trastuzumab. Following completion of all the cycles of trastuzumab treatment, 25/71 patients exhibited pCR (compared to 36/258 patients with pCR in the no-trastuzumab subgroup, P<0.001). The data on neoadjuvant systemic therapy are summarized in Table III and Fig. 1.

Discussion

The results of our unadjusted analyses are in line with previously reported associations between pCR and higher tumor grade and the presence or absence of particular biomarkers. In our multivariate analysis, HER2 amplification, PR status and lack of lymph node involvement were found to be significant predictors of pCR.

Table I. Baseline patient and tumor characteristics.

Characteristics	All patients (n=333)	pCR, no. (%) (n=61)	No pCR, no. (%) (n=272)	P-value
Age, years [median (range)]	48 (20-83)	48 (27-70)	48 (20-83)	0.8
Race				0.9612
Caucasian	233 (70.0)	43 (70.5)	190 (69.9)	
African American	93 (27.9)	17 (27.9)	76 (27.9)	
Other	7 (2.1)	1 (1.6)	6 (2.2)	
Stage				0.0572
II	234 (70.3)	49 (80.3)	185 (68.0)	
III	99 (29.7)	12 (19.7)	87 (32.0)	
Histology				0.0582
IDC	258 (77.5)	56 (91.8)	202 (74.3)	
ILC	22 (6.6)	1 (1.64)	21 (7.7)	
Mixed IDC and ILC	20 (6.0)	1 (1.64)	19 (7.0)	
Inflammatory	18 (5.4)	1 (1.64)	17 (6.2)	
Other	15 (4.5)	2 (3.28)	13 (4.8)	
Grade				0.00065
1 and 2	119 (35.7)	10 (16.4)	109 (40.1)	
3	211 (63.4)	50 (81.96)	161 (59.2)	
Unknown	3 (0.9)	1 (1.64)	2 (0.7)	
Individual biomarkers				
Estrogen				0.026
ER+	174 (52.3)	24 (39.3)	150 (55.15)	
ER-	159 (47.7)	37 (60.7)	122 (44.85)	
Progesterone				0.0007
PR+	147 (44.1)	15 (24.6)	132 (48.5)	
PR-	186 (55.9)	46 (75.4)	140 (51.5)	
HER2				0.0054
HER2+	89 (26.7)	25 (41.0)	64 (23.5)	
HER2-	244 (73.3)	36 (59.0)	208 (76.5)	
Composite biomarkers				0.0007
HR+/HER2+	54 (16.22)	15 (24.6)	39 (14.3)	
HR-/HER2+	35 (10.51)	10 (16.4)	25 (9.2)	
HR+/HER2-	130 (39.04)	10 (16.4)	120 (44.1)	
HR-/HER2-	114 (34.23)	26 (42.6)	88 (32.4)	
Lymph node involvement				0.0004
None	117 (35.14)	25 (41.0)	92 (33.82)	
Any	100 (30.03)	6 (9.8)	94 (34.56)	
Unknown	116 (34.6)	30 (49.2)	86 (31.62)	

pCR, pathological complete response; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Overexpression of HER2, a receptor-like tyrosine kinase, is shared by multiple human carcinomas; however, HER2 amplification in breast cancer is of particular significance in determining therapy and predicting outcome. Present in 20-30% of all breast cancers, HER2 amplification potentiates growth dysregulation, oncogenesis and metastasis, all of which contribute to its association with lower disease-free and overall survival. Tumors that overexpress HER2 are also more likely to be chemoresistant, hence the importance of trastuzumab, a HER2-targeting drug, which was first approved by the Food and Drug Administration in 1998 in the management of these cancers (17). In our study, HER2 overexpression was predictive of pCR in the multivariate model containing individual biomarkers, thus allowing for ER, PR, and HER2

Table II. Unadjusted and multivariate logistic regression analyses identifying independent predictors of pCR following neoadjuvant chemotherapy.

	Unadjusted analyses		Multivariate analysis 1 using composite biomarkers[a]		Multivariate analysis 2 using individual biomarkers	
Variables	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age[b]	0.997 (0.97-1.02)	0.83	0.99 (0.97-1.02)	0.56	0.99 (0.96-1.02)	0.47
ER-	1.00 (reference)				1.00 (reference)	
ER+	0.53 (0.3-0.93)	0.027	-		1.59 (0.64-3.92)	0.32
PR-	1.00 (reference)				1.00 (reference)	
PR+	0.35 (0.18-0.65)	<0.001	-		0.28 (0.11-0.72)	0.0081
HER2-	1.00 (reference)				1.00 (reference)	
HER2+	2.26 (1.26-4.04)	0.0061	-		2.34 (1.23-4.46)	0.0095
Grade 1 and 2	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Grade 3	3.39 (1.65-6.96)	0.0035	2.01 (0.86-4.72)	0.48	2.28 (1.0-5.14)	0.14
Stage II	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Stage III	0.52 (0.26-1.03)	0.060	0.60 (0.27-1.32)	0.096	0.48 (0.23-1.02)	0.057
No LNI	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Any LNI	0.24 (0.092-0.60)	0.0013	0.32 (0.12-0.86)	0.0057	0.28 (0.11-0.79)	0.0039
HR+/HER2+	1.00 (reference)				1.00 (reference)	
HR+/HER2-	0.21 (0.078-0.55)	<0.001	0.27 (0.11-0.67)	0.0045	-	
HR-/HER2+	0.96 (0.37-2.47)	0.099	0.95 (0.34-2.65)	0.20	-	
HR-/HER2-	0.74 (0.31-1.74)	0.43	0.59 (0.26-1.33)	0.84	-	

[a]The composite biomarkers assessed in regression model were HR+/HER2+, HR+/HER2-, HR-/HER2+ and HR-/HER2-. [b]Analyzed as a continuous variable. pCR, pathological complete response; OR, odds ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LNI, lymph node involvement.

Table III. Neoadjuvant systemic therapy received based.

Characteristics	All patients (n=333)	pCR no. (%) (n=61)	No pCR no. (%) (n=272)	P-value
Trastuzumab therapy				<0.001
Yes	71 (21.3)	25 (41.0)	46 (16.9)	
No	258 (77.5)	36 (59.0)	222 (81.6)	
Unknown	4 (1.2)	0 (0.0)	4 (1.5)	
Chemotherapy grouping				0.0161
Anthracyclines and taxanes	252 (75.7)	46 (75.4)	206 (75.7)	
Anthracycline-based	19 (5.7)	0 (0.0)	19 (7.0)	
Taxane-based	48 (14.4)	14 (23.0)	34 (12.5)	
Platinum agent-based	4 (1.2)	1 (1.6)	3 (1.1)	
Unknown	10 (3.0)	0 (0.0)	10 (3.7)	

pCR, pathological complete response.

statuses to be directly controlled for in relation to one another. In the model with composite biomarkers, we also observed that the ER+/PR+/HER2- subtype was negatively associated with pCR. The aggregate of these findings suggests that there may be a complex interplay between the tumor biology and treatment with trastuzumab. In reference to pCR rates, we are currently unable to disentangle the potential biological effects of HER2 amplification from the potential benefits gained from trastuzumab treatment. Additional prospective studies are required to elucidate this matter.

Lack of lymph node involvement was also found to be a significant predictor of pCR in patients with HER2 amplification

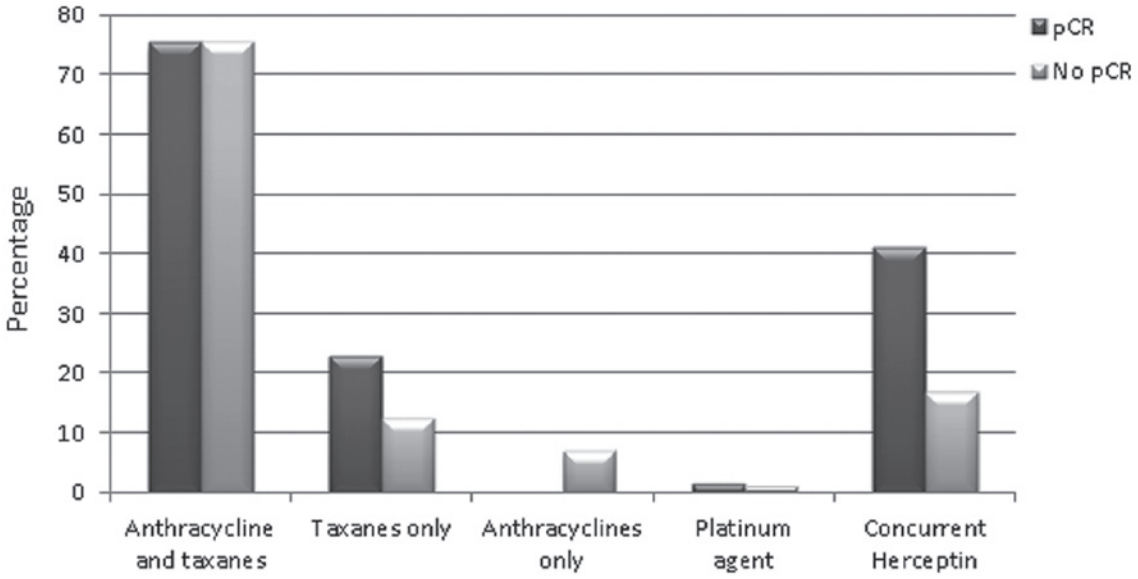

Figure 1. Chemotherapeutic regimen used in patients with or without pathological complete response (pCR).

without ER or PR expression, even after adjusting for stage in the regression model. Lymph node involvement at initial presentation is a well-established outcome prognosticator in breast cancer and patients with breast pCR but residual nodal disease have lower rates of overall survival compared with patients who experience breast as well as nodal pCR (1,18).

The assessment of the type of neoadjuvant systemic therapy received, highlights the fact that the majority of the treated patients at our institution received the standard recommended regimen, while also exhibiting improved pCR rates when taxanes are used or added to anthracycline therapy. Multiple trials evaluating a broad range of chemotherapy drugs have also demonstrated that the use of anthracyclines in combination with taxanes is associated with improved pCR rates (7,10). Hence, the consensus statement of the St. Gallen Conference, states that a standard neoadjuvant chemotherapy regimen should include both an anthracycline and a taxane (19).

Platinum agents are DNA-damaging agents, which have been found to be particularly beneficial in improving pCR rates in triple-negative breast cancer (TNBC), particularly BRCA-mutated tumors (which represent up to 50% of all TNBCs). In a meta-analysis of 28 studies, the pooled pCR rate noted following addition of a platinum agent to a standard neoadjuvant chemotherapy regimen for TNBC was 45% (20). Another single-institution study reported pCR rates of 22% following neoadjuvant treatment with single-agent cisplatin therapy in patients with stage II or III TNBC (21). In our study, all 4 patients receiving platinum agents had TNBC and they received single-agent therapy with the platinum agent. Of note, the sole patient exhibiting pCR following administration of the platinum agent had a higher tumor grade (grade 3), lower stage (stage II) and no lymph node involvement. To the best of our knowledge, a review of the literature has retrieved no data to suggest that the improvement in pCR rates following addition of platinum agents to standard neoadjuvant chemotherapy in TNBC translates to improvements in overall survival or disease-free survival. More studies are required to evaluate the potential survival benefits of adding platinum-based therapy to standard neoadjuvant chemotherapy for patients with TNBC.

Our study had certain limitations. First, we were unable to establish causation, but could only show association, due to the fact that retrospective studies are prone to patient and treatment selection bias. Additionally, potential confounding variables may not always be recognized or recorded, due to a lack of knowledge regarding how they interact with the outcome of interest. Second, we were unable to control for administration of trastuzumab therapy with regard to the association of HER2 amplification with pCR. As the provision of HER2-targeted therapy has recently become more standardized, future prospective studies will undoubtedly be better equipped to investigate this issue. Third, all the patients in our study were treated at a high-volume, NCI-designated comprehensive cancer center, although the majority of the patients in this country obtain their chemotherapy from non-academic, community medical oncologists. This may translate to potential differences in patient population, treatment received, treatment duration, or even the definition of pCR; thus, the extent to which our patients exhibit pCR and the reasons why they do so, may not reflect the experience of breast cancer patients receiving care outside a comprehensive cancer center. Finally, details regarding the optimal chemotherapy dose, treatment duration, or concurrent vs. sequential administration for improving pCR rates were not obtained in this study. Other studies are currently underway, however, to address optimal administration times in the neoadjuvant setting to improve pCR rates.

In conclusion, we found in the regression model using the composite HR variable that HR+/HER2- tumors were significantly less likely to undergo pCR compared with HR+/HER2+ tumors, and that tumors with any lymph node involvement were significantly less likely to undergo pCR compared with tumors without lymph node involvement. Additionally, we found that the pCR rates were higher among patients receiving trastuzumab or taxane therapy in addition to anthracycline therapy.

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