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PREDICTORS OF COMPLETE PATHOLOGIC RESPONSE AFTER NEOADJUVANT SYSTEMIC THERAPY FOR BREAST CANCER

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Abstract

Background—The current study aim was to identify predictors of pathologic complete response (pCR) following neoadjuvant therapy.

Methods—From 2000-2007, 518 breast cancer patients received neoadjuvant therapy. Data were compared using Chi-square, Fisher's exact test, and MANOVA, where appropriate.

Results—Of 518 breast cancer patients receiving neoadjuvant therapy, 81 (16%) had a pCR [77 of 456 (17%) chemotherapy; 4 of 62 (6%) endocrine therapy; $p < 0.05$]. Four factors were associated with pCR: higher tumor grade ($p = 0.015$), lack of estrogen and progesterone receptor (ER/PR) expression ($p < 0.0001$), HER-2/neu amplification ($p = 0.025$), and negative lymph node status ($p < 0.0001$). On multivariate analysis, ER/PR negativity, HER-2/neu amplification, and negative lymph node status were found to significantly correlate with pCR.

Conclusions—Patients with ER/PR negative and Her-2/neu amplified breast cancer phenotypes are more likely to experience a pCR to neoadjuvant therapy. While a pCR is more frequently observed following neoadjuvant chemotherapy, it is rare following neoadjuvant endocrine therapy.

Keywords

Breast cancer; Neoadjuvant therapy; Pathologic response

INTRODUCTION

Neoadjuvant therapy is the standard of care for the management of locally advanced breast cancer, and is increasingly being used for the treatment of early-stage disease(1). By reducing tumor volume, it has been shown to increase rates of breast conserving surgery, and has additional theoretical advantages including treatment of undetected micrometastatic disease, and allowing early assessment of response to chemotherapy(2).

A small but consistent proportion of patients treated with neoadjuvant therapy have been observed to have a pathologic complete response (pCR) (3, 4). There has, as a result, been

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much interest in identifying these patients a priori (2, 5-11). The purpose of this study was to identify clinical and pathologic factors associated with a pCR following neoadjuvant therapy in patients with breast cancer treated at our institution. Unique to this study was the inclusion of patients undergoing both neoadjuvant systemic chemotherapy as well as neoadjuvant endocrine therapy.

METHODS

Study Design

Institutional review board approval was obtained prior to the commencement of this retrospective study. Written informed consent of patients was not required. The prospectively maintained surgical database at Washington University/Barnes Jewish Hospital was queried from January 1, 2000 to December 31, 2007 to identify all patients with a diagnosis of Stage I-III [according to American Joint Committee on Cancer guidelines (12)] biopsy-proven invasive breast cancer who underwent neoadjuvant chemotherapy or endocrine therapy (n=603). Patients were excluded if they had incomplete hormone receptor and/or HER-2/neu status information. Thus, 518 patients were included in the analysis.

Pathologic Assessment

Pathologic diagnosis, estrogen receptor (ER) status, progesterone receptor (PR) status, and HER-2/neu status were determined by core biopsy prior to neoadjuvant therapy. ER and PR status were determined by standard immunohistochemical methods. Tumors with greater than 10% stained cells were considered to have positive receptor status. All patients had HER-2/neu status assessed by fluorescence in situ hybridization (FISH). A pCR was determined by microscopic examination of the excised tumor and lymph nodes after completion of therapy, and defined as the disappearance of all invasive disease from the breast and lymph nodes. Patients who had only ductal carcinoma in situ (DCIS) in the breast tissue following neoadjuvant therapy were considered to have a pCR.

Statistical Analyses

Categorical data were compared using Fisher's exact and chi squared tests. P values <0.05 were considered statistically significant. All P values were two-tailed. Univariate analysis was used to estimate the effects of clinical and pathologic characteristics on response to neoadjuvant therapy. To identify variables independently associated with a pCR, a multivariate analysis using MANOVA was performed. All variables with a P value < 0.20 in the univariate analysis were included in a logistic regression model, allowing for interaction. Overall survival, defined from the date of diagnosis to the date of death from any cause, was estimated with the Kaplan-Meier method. All analyses were performed with SAS version 9 (SAS Institute).

RESULTS

Over the period 2000-2007, 603 patients with breast cancer were treated with neoadjuvant therapy. Of these, 518 had complete hormone receptor and HER-2/neu amplification status, and were therefore included for subsequent analysis. Patient and tumor characteristics are shown in Table 1. The median patient age at the time of diagnosis was 52 years (range: 24-87). The majority of patients were Caucasian (69%), with 178 being African American (29%). Median follow-up was 44 months (range 3-133 months).

The median tumor size was 3.8 cm. The majority of patients had T2 tumors (54%), with 12% having T1 tumors, 18% having T3 tumors, and 16% having T4 tumors. The vast

majority of patients had ductal carcinoma (72%), with lobular, mixed and miscellaneous histologies each comprising 10%. Only 10% of tumors were well-differentiated, with 34% being moderately-well differentiated, and 56% being poorly differentiated. Lymphovascular invasion was present in 19%. Of patients with positive nodal status, most were N1. With regard to clinical stage, 64% of patients were stage 2A or 2B, with 30% of patients being stage 3A or higher.

With regard to hormone receptor status, 58% of patients were ER positive, and 42% were PR positive. The proportion of patients who were therefore double negative (ER negative and PR negative) was 41%. HER-2/neu gene amplification was detected in 148 patients (26%).

The majority of patients received neoadjuvant chemotherapy (88%), and the remaining patients received neoadjuvant endocrine therapy (12%). Overall, following neoadjuvant therapy, 60% of patients underwent mastectomy, with the remaining 40% having breast-conserving surgery. Upon pathologic review of tumor and nodal specimens, 81 of the 518 patients (16%) were found to have had a pCR. Of the 81 patients with a pCR, 77 (95%) occurred following neoadjuvant chemotherapy and 4 (5%) occurred following neoadjuvant endocrine therapy. In the total cohort, there were 155 patients with ER negative, PR negative and HER-2/neu non-amplified breast cancers [“triple negative breast cancer (TNBC)”], 58 patients with HER-2/neu amplified/ER negative breast cancers (“HER-2+”), and 305 patients with ER positive and/or PR positive breast cancers (“luminal” subtype). A pCR occurred in 23% of TNBC, 31% of HER2+, and 10% of luminal subtypes ($P < 0.0001$).

Table 2 is a summary of the relationship between clinico-pathologic factors and pCR. On univariate analysis, factors associated with an increased percentage of pCR include high tumor grade ($p = 0.015$), double negative hormone receptor status ($p < 0.0001$), HER-2/neu gene amplification ($p = 0.025$), and N0 nodal status pre-therapy ($p < 0.001$). On multivariate analysis, only hormone receptor status (odds ratio [OR] 2.8, $p = 0.012$), HER-2/neu amplification (OR 2.2, $p = 0.022$) and N0 nodal status pre-therapy (OR 0.2, $p < 0.0001$) were independent predictors of complete pathologic response.

Overall survival was not significantly different between the 81 patients with pCR and the remaining 437 patients with residual disease (Figure 1). Further sub-group analysis of the overall survival of the patients with pCR showed that there was no significant difference according to hormone status or HER-2/neu amplification status (Figure 2).

DISCUSSION

This study reports outcomes of patients with breast cancer treated with neoadjuvant therapy from a large, single-institution series. An analysis was performed to identify clinico-pathologic factors associated with complete pathologic response. Three independent factors were found: hormone receptor status, HER-2/neu amplification status and nodal status. No survival benefit of pCR was observed over the median 44 month follow-up.

In clinical trials of neoadjuvant chemotherapy, the pCR has ranged from 6-26% (4, 13-16). In our study, the pCR for patients treated with neoadjuvant chemotherapy was found to be 16%, which is the same as for another large, single-institution retrospective analysis by Liedtke et al (3). In contrast, it appears that pCRs occur infrequently with neoadjuvant endocrine therapy. The pCR rates for tamoxifen and letrozole in the P024 trial were $< 1\%$, despite much higher clinical objective response rates (17). Four of the sixty-two patients in our study who were treated with neoadjuvant endocrine therapy demonstrated pCR.

The importance of a pCR lies in the fact that large clinical trials of neoadjuvant chemotherapy have demonstrated that patients with pCR have an improved disease-free survival (DFS) and overall survival (OS) compared to those with residual disease. In Protocol B-18 of the National Surgical Adjuvant Breast and Bowel Project (NSABP), patients who achieved a pCR had DFS and OS of 75% and 85%, respectively, at median follow-up of 9.9 years, compared with 58% and 73% for patients with residual disease (18). Similar results have been demonstrated in NSABP Protocol B-27 (4). This has led to interest in using pCR as a surrogate clinical endpoint for the testing of new chemotherapeutic regimens, thereby shortening the required duration of follow-up for analysis of these trials (19). In our study, the absence of a survival advantage for patients with pCR versus those with residual disease may be due to small sample size, short follow-up, and the inclusion of patients treated with neoadjuvant endocrine therapy.

There have been a number of reports analyzing factors associated with pCR after neoadjuvant therapy. Prior to the era of routine testing for hormone receptors, both NSABP B-18 and B-27 demonstrated a strong association ($p < 0.0001$) between pathologic response and nodal status, with the group of patients with pCR being more frequently node-negative (4, 20). This was corroborated by the current study. Kuerer et al. (21) found that patients with a smaller clinical T size prior to chemotherapy had a higher rate of pCR. Clinical T size was not a significant predictive factor for pCR in our patient population. The reasons for this are unclear. In the Kuerer et al. (21) cohort, 30% of patients had a clinical T3 and 39% of patients had a clinical T4 breast cancer at diagnosis. This is dramatically different from our cohort where 11% of patients had T1 tumors and 52% of patients had T2 tumors. This predominance of smaller T1/T2 lesions in our study may account for this difference. It is also possible that our inclusion of neoadjuvant endocrine therapy in addition to neoadjuvant chemotherapy contributed to this finding.

Subsequently, multiple studies, both clinical trials and retrospective analyses, have shown a negative association between hormone receptor expression and pCR (13, 16, 22-25). For example, in the European Cooperative Trial in Operable breast cancer (ECTO), on multivariate analysis, ER status was found to be the only independent variable associated with achieving a pCR (odds ratio 5.77, $p < 0.0001$) (22). These findings were confirmed in a large study by Berry et al (26). Further, Colleoni et al (6) demonstrated that patients with ER and PR negative tumors more commonly achieved pCR than those with ER and/or PR positive tumors (23% vs. 7%, respectively; $P = 0.04$).

While HER-2/neu amplification is well-known to be a negative prognostic factor, there are conflicting reports concerning its role as a predictive factor for response to neoadjuvant chemotherapy (7, 8, 11, 27-29). For example, in evaluating anthracycline and taxane neoadjuvant chemotherapy, Tiezzi et al (11) were unable to demonstrate an association between HER-2/neu amplification and pathologic response, whereas studies by Rouzier et al (28) and Rody et al (8) found that HER-2/neu amplification was highly predictive of pathologic response. The current study supports the finding that patients with HER-2/neu amplified breast cancers are more likely to experience a pCR than patients with HER-2/neu non-amplified breast cancers. This finding is likely dependent on the use of a trastuzumab-containing neoadjuvant regimen, though we are unable to confirm that all patients received such treatment in this retrospective analysis.

At the same time, however, we observed that those patients with TNBC [also termed “basal-like”(30)] are more likely to achieve pCR than non-TNBC (23% versus 10%, respectively). This is consistent with recent work by other groups (3, 5). In particular, Carey et al (5), in their study of 107 patients, found that it was two hormone receptor-negative subtypes (TNBC and HER2+) that displayed much higher rates of pCR (27% and 36%, respectively),

compared to the luminal subtype, which had a pCR rate of 7% ($P=0.01$). These findings concur very closely with those reported here. The TNBC and HER2+ breast cancer subtypes are characterized by a high proliferation index which may account for an increased sensitivity to chemotherapy.

This study has a number of limitations. It is a retrospective analysis, with median follow-up of less than 4 years. The patient sample is heterogeneous with regard to stage, histology, and neoadjuvant protocol utilized. The patients underwent many variable neoadjuvant chemotherapy or endocrine therapy regimens based on individual patient and tumor characteristics. Further, the extended time period over which the patients were accrued to the neoadjuvant protocols could contribute to the pCR rate as improvements in chemotherapy and hormonal therapy have been observed over the study period. We are unable to control for these variations in the current retrospective analysis. These limitations may explain the lack of an observed difference in overall survival between the patients with a pCR and those with residual disease. In addition, we are unable to determine the decisions that resulted in our patients undergoing neoadjuvant therapy. At our institution, approximately 50% of patients undergoing neoadjuvant therapy have locally advanced disease and are not considered candidates for breast-conserving procedures, regardless of response to therapy. The remaining 50% undergo neoadjuvant therapy in hopes of achieving breast conservation. Based on the clinical T stages prior to therapy, approximately 60% of patients had T1/T2 lesions and breast conservation would be expected. Only 40% of the total group, however, underwent breast-conserving surgery. We cannot account for the patient factors and surgeon recommendations that may account for this discrepancy in this retrospective study.

In spite of this lack of some potentially relevant information, the current study represents a large, single-institution cohort analysis of patients undergoing neoadjuvant therapy for breast cancer. The fact that hormone receptor status, HER-2/neu amplification status and nodal status remain independent predictors of a pCR, despite the heterogeneity of the patient population, emphasizes their importance.

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SUMMARY

Patients with estrogen and progesterone receptor negative breast cancers with or without HER-2/neu amplification are more likely to experience a pathologic complete response to neoadjuvant chemotherapy. A pathologic complete response following neoadjuvant endocrine therapy is less common.

Figure 1.
Overall survival comparing patients with a pathologic complete response (“Y”, n=81) and those with residual disease (“N”, n=437).

Figure 2.

Sub-group analysis of 81 patients with pCR, comparing overall survival according to (A) estrogen receptor status ("Y" = estrogen receptor positive; "N" = estrogen receptor negative; $p=0.11$); (B) progesterone receptor status ("Y" = progesterone receptor positive; "N" = progesterone receptor negative; $p=0.38$); and (C) HER-2/neu amplification status ("Y" = amplified; "N" = non-amplified; $p=0.098$).

Table 1

Patient and tumor characteristics of 518 patients undergoing neoadjuvant therapy for breast cancer.

Characteristic	N (%)
Age	
<50	261 (50%)
50	257 (50%)
Race	
Caucasian	357 (69%)
African-American	149 (29%)
Other	12 (2%)
Clinical T stage	
T1	59 (11%)
T2	268 (52%)
T3	90 (17%)
T4	80 (16%)
Unknown	21 (4%)
Histology	
Ductal carcinoma	379 (72%)
Lobular carcinoma	51 (10%)
Inflammatory	35 (7%)
Mixed (ductal+lobular)	37 (7%)
Other	16 (4%)
Nuclear grade	
Grade 1 (well differentiated)	51 (10%)
Grade 2 (moderately differentiated)	170 (33%)
Grade 3 (poorly differentiated)	282 (54%)
Unknown	15 (3%)
Estrogen receptor status	
Positive	298 (58%)
Negative	220 (42%)
Progesterone receptor status	
Positive	219 (42%)
Negative	299 (58%)
HER2-neu status	
Non-amplification	384 (74%)
Amplification	134 (26%)
Clinical N status	
N0	237 (46%)
N1	210 (41%)
N2	28 (5%)
N3	14 (3%)
Unknown	29 (5%)
Clinical AJCC stage	

Characteristic	N (%)
1	32 (6%)
2A	177 (35%)
2B	145 (28%)
3A	52 (10%)
3B	69 (13%)
3C	12 (2%)
4	13 (3%)
Unknown	18 (3%)
Type of neoadjuvant therapy	
Chemotherapy only	456 (88%)
Hormonal therapy	62 (12%)
Type of surgery performed on primary tumor	
Lumpectomy	207 (40%)
Mastectomy	311 (60%)
Pathologic complete response	
Yes	81 (16%)
No	437 (84%)

AJCC = American Joint Commission on Cancer

Table 2

Univariate Predictors of Pathologic Complete Response to Neoadjuvant Therapy for Breast Cancer

Characteristic	P value
Race	0.287
Increasing tumor grade	0.015
Clinical T stage	0.231
ER / PR negative status	0.00002
HER-2/neu amplification	0.025
Clinical N0 nodal status	< 0.0001
Use of chemotherapy vs. endocrine therapy	0.081

Table 3

Multivariate Predictors of Pathologic Complete Response to Neoadjuvant Therapy for Breast Cancer

Characteristic	Odds Ratio			P value
	Point estimate	95% confidence limits		
ER / PR negative status	2.80	1.25	6.29	0.012
HER-2/neu amplification	2.21	1.12	4.35	0.022
N0 nodal status	0.18	0.093	0.341	< 0.0001