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CLINICAL TRIAL

Patient and tumor characteristics associated with breast cancer recurrence after complete pathological response to neoadjuvant chemotherapy

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Abstract Breast cancer patients whose tumors achieve a pathological complete response (pCR) with neoadjuvant chemotherapy have a prognosis which is better than that predicted for the stage of their disease. However, within this subgroup of patients, recurrences have been observed. We sought to examine factors associated with recurrence in a population of breast cancer patients who achieved a pCR with neoadjuvant chemotherapy. A retrospective chart review was conducted of all patients with unilateral breast cancer treated with neoadjuvant chemotherapy from January 1, 2000 to December 31, 2010 at one comprehensive cancer center. A pCR was defined as no residual invasive cancer in the breast in the surgical specimen following neoadjuvant therapy. Recurrence was defined as visceral or bony reappearance of cancer after completion of all therapy. Of 818 patients who completed neoadjuvant chemotherapy, 144 (17.6 %) had pCR; six with bilateral breast cancer were excluded from further analysis. The mean time to follow-up was 47.2 months. Among the 138 patients with unilateral breast cancer, there were 14 recurrences (10.1 %). Using a binary multiple logistic regression model, examining types of chemotherapy and surgery, race, lymph node assessment, and lymph node status, breast cancer side, triple-negative status, and radiation receipt, only African-American patients (OR: 5.827, 95 % CI: 1.280–26.525; $p = 0.023$) were more likely to develop distant recurrence. The mean time to recurrence was 31.9 months. In our study, race was the only independent predictor of recurrence after achieving pCR with neoadjuvant chemotherapy. The reasons for this observation require further study.

Keywords Neoadjuvant chemotherapy · Breast cancer · Complete pathological response · Recurrence

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Introduction

Breast cancer is the second most common cancer in women, with 1 in 8 women in the U.S. being diagnosed during their lifetime [1]. Fortunately, treatment of breast cancer has evolved, leading to improvement in disease-free survival and overall survival rates, especially in patients with tumors that were previously believed to be incurable. Neoadjuvant chemotherapy, also known as primary systemic therapy, has been used to treat systemic disease with the desired goal of improving survival as well as downsizing tumors to reduce the extent of surgery. Neoadjuvant chemotherapy has been shown to be particularly beneficial in patients with inoperable locally advanced or inflammatory and large operable breast cancers [2–6]. Patients with smaller breast tumor sizes of 1–2 cm have also been shown to benefit from neoadjuvant chemotherapy [5, 7–10].

Clinically, neoadjuvant chemotherapy has been correlated with high tumor regression rates resulting in increased breast-conserving surgery, improvements in the proportion of patients who have axillary lymph nodes

without metastases, and prolonged rates of disease-free survival and overall survival benefits, especially in patients who achieve a pathological complete response (pCR) of their tumors [5–13]. As a result, those patients whose tumors are able to achieve a pCR with neoadjuvant chemotherapy have been reported to have a better prognosis than their initial staging would predict. However, within the population of patients who have had a pCR, a subset has been observed to develop distant recurrent disease [9, 14–17].

To identify those patients at risk for recurrence after achieving a pCR with neoadjuvant chemotherapy, we have reviewed tumor biomarkers and clinical characteristics of breast cancer patients who recurred versus those who did not recur in a population of patients who achieved a pCR with neoadjuvant chemotherapy.

Methods

We conducted a retrospective chart review of all breast cancer patients treated with neoadjuvant chemotherapy from January 1, 2000 to December 31, 2010 at a single National Cancer Institute-designated comprehensive cancer center after IRB approval. A pCR was defined as having no residual invasive tumor in the breast surgical specimen removed following neoadjuvant therapy; patients with residual carcinoma in situ were considered to have a pCR. Recurrence was defined as visceral or bony reappearance of cancer after completion of all therapy. We gathered data on tumor characteristics (size, grade, estrogen-receptor, progesterone-receptor, and human epidermal growth factor receptor 2([Her2] status, breast side, tumor type), type of surgery, having any lymph node assessment, lymph node status, recurrence status, receipt of radiation treatment, chemotherapy type, and demographic information (race and age) by chart review. Pre-treatment tumor size was determined by radiographic measurements. Magnetic-resonance imaging (MRI) measurements were used if they were available. If MRI was not performed then, ultrasound measurements were used. If MRI and ultrasound measurements were not performed, then the mammographic measurements were used. The longest diameters were used in the analysis.

Data were analyzed using SPSS version 20; two-tailed tests at $p < 0.05$ were considered significant. We used one-way analysis of variance to test the association between patient age at diagnosis and recurrence; we used χ^2 tests of significance to examine each of the categorical variables in association with recurrence. After examining the univariate associations between the various demographic and clinical variables, a binary, multivariate logistic regression analysis was performed with selected variables to identify independent predictors of risk of recurrence in patients who achieved a pCR after receiving neoadjuvant chemotherapy.

Results

Of 818 patients who had received neoadjuvant chemotherapy, 144 (17.6 %) had a pCR in the breast; six of these 144 patients had bilateral breast cancer and were excluded from the analysis. Among the remaining 138 patients, there were 14 recurrences (10.1 %). Descriptive statistics of the sample of patients are shown in Table 1. Eighty-six percent (119/138) of the primary cancers were invasive ductal carcinomas, and 78 % (107/138) were grade III tumors; 67 % were estrogen-receptor negative, 80 % were progesterone-receptor negative, and 60 % were HER2-receptor negative. The mean time to follow-up was 47.2 months (range, 3.1–140.5 months).

Of the 14 patients with recurrent disease, eight (57 %) were Caucasian and six (43 %) were African-American; 71 % of patients with recurrence had invasive ductal carcinomas, and 64 % of the tumors were grade III; 67 % of the recurrent cases involved estrogen-receptor negative tumors, 80 % involved progesterone-receptor negative tumors, 60 % involved HER2-positive tumors, and 42 % were triple-negative tumors. Eleven of the patients had recurrences to the viscera, while three had recurrences to the viscera and bone. One of the patients not only had a chest wall recurrence but also had recurrences in the lymph nodes and colon. The mean time to recurrence was 31.9 months (range, 1.6–88.3 months).

The mean (SD) tumor sizes are shown in Table 2; 10 women missing tumor size data (five of them with inflammatory breast cancer) were excluded from analysis of tumor size. As shown in Table 2, there was no significant difference in tumor size between women with and women without a recurrence ($p = 0.881$). However, tumor size differed significantly by race, with patients of other race having significantly larger tumors compared with Caucasian and African-American patients ($p = 0.028$).

In the multivariate logistic regression model, we examined the following factors in association with recurrence: type of chemotherapy, type of surgery, race, lymph node status, breast cancer side, triple-negative status, lymph node assessment, and receipt of radiation therapy. In this adjusted model, only patients who were African-American (OR: 5.827, 95 % CI: 1.280–26.525; $p = 0.023$) were more likely to develop recurrence (Table 3; Fig. 1).

Of all 53 patients who had HER2-positive tumors, 15 patients did not receive trastuzumab. We further examined whether the greater likelihood of recurrence among African-American patients might have been due to a lower likelihood of receipt of trastuzumab among African-American

Table 1 Patient and tumor characteristics in patients who achieved a pCR with neoadjuvant chemotherapy

	Total $N = 138$	Recurrence 14 (%)	No recurrence 124 (%)	p value[a]
Mean (SD) age at diagnosis (years)	137	54.1 (10.4)[b]	50.6 (10.2)	0.253[c]
Race				0.320
Caucasian	94	8 (57)	86 (69)	
African-American	38	6 (43)	32 (26)	
Other	6	0 (0)	6 (5)	
Pathology				
Ductal carcinoma	119	10 (71)	109 (88)	0.090
Lobular and other carcinoma	19	4 (29)	15 (12)	
Grade				
I	2	0 (0)	2 (2)	0.323
II	22	3 (21)	19 (15)	
III	107	9 (64)	98 (79)	
Unknown	7	2 (14)	5 (4)	
Laterality				
Right	64	9 (64)	55 (44)	0.156
Left	74	5 (36)	69 (56)	
Surgery type				0.159
Breast-conserving surgery	67	4 (29)	63 (51)	
Mastectomy	71	10 (71)	61 (49)	
Lymph node assessment				0.828
Yes	126	13 (93)	113 (91)	
No	12	1 (7)	11 (9)	
Lymph node status				0.809
Positive	80	9 (64)	71 (57)	
Negative	56	5 (36)	51 (41)	
Unknown	2	0 (0)	2 (2)	
Radiation receipt				0.143
Yes	120	10 (71)	110 (89)	
No	17	4 (29)	13 (10)	
Unknown	1	0 (0)	1 (1)	
Chemotherapy type				0.901
Adriamycin and taxane	59	6 (43)	53 (43)	
Adriamycin	15	2 (14)	13 (10)	
Other	64	6 (43)	58 (47)	
Estrogen status				0.131
Positive	44	3 (21)	41 (33)	
Negative	92	10 (71)	82 (66)	
Unknown	2	1 (7)	1 (1)	
Progesterone status				0.094
Positive	26	4 (29)	22 (18)	
Negative	110	9 (64)	101 (81)	
Unknown	2	1 (7)	1 (1)	
Her-2 status				0.848
Positive	53	6 (43)	47 (38)	
Negative	83	8 (57)	75 (60)	
Unknown	2	0 (0)	2 (2)	
Triple-negative status				0.115
Triple negative	58	4 (29)	54 (44)	

Table 1 continued

	Total $N = 138$	Recurrence 14 (%)	No recurrence 124 (%)	p value[a]
Not triple negative	78	9 (64)	69 (56)	
Unknown	2	1 (7)	1 (1)	

Percentages may not total 100 due to rounding

SD standard deviation. *HER-2* human epidermal growth factor receptor 2

[a] Tests of significance are χ^2, except where noted

[b] One patient did not have date of birth to calculate age at diagnosis, so mean computed based on 13 patients

[c] Test of significance is one-way analysis of variance

Table 2 Mean tumor size and 95 % confidence interval (CI) in 128 patients who achieved a pCR with neoadjuvant chemotherapy[a]

	$N = 128$	Mean (95 % CI) size, in cm	p value[b]
Recurrence			0.881
Yes	11	3.391 (2.366–4.416)	
No	117	3.310 (2.996–3.624)	
Race			0.028
Caucasian	86	3.261 (2.903–3.619)	
African-American	36	3.150 (2.597–3.703)	
Other	6	5.117 (3.762–6.471)	

[a] Ten women were missing tumor size data

[b] One-way analysis of variance

patients with HER2-positive tumors compared with Caucasian patients. In an unadjusted binary logistic regression model including only these 53 patients, neither trastuzumab use (OR: 0.308, 95 % CI: 0.017–5.497), nor race (African-American vs. Caucasian OR: 4.000, 95 % CI: 0.273–58.562; other race vs. Caucasian, unable to be computed for $n = 3$), nor the interaction between trastuzumab use and race (OR: 2.167, 95 % CI: 0.053–88.383) was significantly associated with recurrence.

Discussion

Knowledge about factors associated with breast cancer recurrence in patients achieving a pCR after neoadjuvant chemotherapy remains limited. Approximately 15–30 % of women achieve a pCR with neoadjuvant chemotherapy and a significant number of these women will develop recurrent disease. In our study, 10.1 % of women who achieved a pCR with neoadjuvant chemotherapy developed distant recurrence of their cancer with a mean time to recurrence of 31.9 months. We found that those patients who were African-American were at a higher risk of recurrence.

Neoadjuvant chemotherapy is recommended for a variety of reasons. Neoadjuvant chemotherapy has been shown to decrease the size of the primary breast tumor allowing for more women to become candidates for breast-conserving surgery, and it has also been hypothesized to reduce the number of micrometastases [21–25]. A pCR has been used as a possible surrogate for efficacy of the treatment. In addition, there is a small possibility that surgical resection may cause the seeding of tumor cells, promoting micrometastases [21–25]. Neoadjuvant chemotherapy may prevent recurrences by reducing the likelihood that tumor cells will be released during surgery.

Rates of pCR with neoadjuvant chemotherapy vary depending on the tumor subtype and treatment. In our patient population, 18 % of women achieved a pCR after neoadjuvant chemotherapy. This percentage is similar to that reported in the studies of Gonzalez-Angulo et al. [14] and Tanioka et al. [15], which showed that 16 and 20 % of women achieved a pCR after neoadjuvant chemotherapy, respectively (Table 4).

Though pCR has been considered to be a possible surrogate for disease-free survival, recurrence rates in these women have been reported to range from 10 to 40 %. Fisher et al. [9] reported recurrence rates of 28.3–39.7 % at 5 years in 89 patients who received neoadjuvant chemotherapy patients with pCR. Another study of 138 patients reported by Gajdos et al. [16] found that 18 patients had a pCR and observed a 41 % 5-year recurrence rate in these patients with pCR. Kuerer et al. [17] showed that the mean time to recurrence for patients with complete response to neoadjuvant chemotherapy was 25 months, with local recurrence occurring in 5 % and distant recurrence in 12 % of patients. We observed a 10.1 % recurrence rate in patients with pCR with a mean follow-up of 31.9 months which is slightly lower than that observed in other studies and may be due to the shorter period of follow-up [9, 16, 17].

We found that African-American patients were more than five times more likely to develop recurrence of their cancer after controlling for other clinical and demographic variables. This finding is consistent with larger analyses of breast cancer in racial minorities, in which African-American patients are noted to be more likely to develop cancer in the under-35 age group [18], more likely to be diagnosed with large tumors and distant-stage disease [19],

Table 3 Multivariable logistic regression model of factors associated with recurrence

Parameters	*N*	OR (95 % CI)	*p* value
Type of Chemotherapy			
Adriamycin and taxane	59	1.000	
Adriamycin Alone	15	1.349 (0.188–9.684)	0.766
Other	64	0.717 (0.179–2.880)	0.639
Race			
Caucasian	94	1.000	
African-American	38	5.827 (1.280–26.525)	0.023
Other[a]	6	0 (0)	0.999
Lymph node assessment			
No	12	1.000	
Yes	126	0.437 (0.027–7.165)	0.562
Radiation therapy			
No	17	1.000	
Yes	120	0.259 (0.051–1.330)	0.106
Unknown[a]	1	0 (0)	1.000
Breast cancer side			
Right	64	1.000	
Left	74	0.478 (0.132–1.729)	0.260
Lymph node status			
Negative	56	1.000	
Positive	80	1.338 (0.297–6.028)	0.704
Unknown[a]	2	0 (0)	0.999
Triple-negative status			
Negative	78	1.000	
Positive	58	0.650 (0.149–2.838)	0.567
Unknown	2	19.384 (0.752–499.544)	0.074
Type of surgery			
Breast-conserving surgery	67	1.000	
Mastectomy	71	4.187 (0.858–20.431)	0.077

OR odds ratio, *CI* confidence interval

[a] OR and 95 % CI not calculated due to small *n*

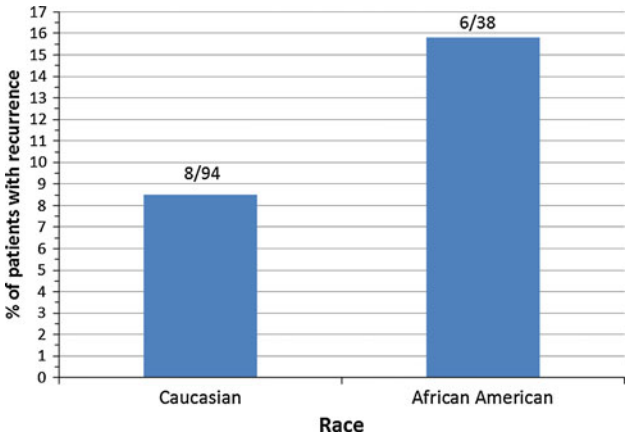


Fig. 1 Percentage of patients with recurrence. A greater proportion of African-American patients had a breast cancer recurrence after achieving a pCR with neoadjuvant chemotherapy treatment compared with the proportion of Caucasian patients

and more likely to die from breast cancer [20]. The reasons for disparities in breast cancer outcomes among African-American patients have not been fully explained and require continued investigation to determine whether the disparities in survival reflect the socioeconomic disparities or true biological differences that affect response to therapy in breast cancers.

Two other studies have examined predictors of recurrence in patients with pCR after neoadjuvant chemotherapy treatment. Gonzalez-Angulo et al. [14] found that menopausal status, breast cancer stage, and the number of lymph nodes samples were associated with increased likelihood of breast cancer recurrence. Tanioka et al. [15] showed that axillary lymph node metastasis and HER2 status were predictive factors for recurrence. While our study included lymph node status, lymph node assessment, and triple-negative status, these factors were not found to be

Table 4 Studies on predictors of recurrence after achievement of pCR after neoadjuvant chemotherapy

Author(s)	Year of publication	# of patients	# of patients with pCR	Factors included in analysis
Gonzalez-Angulo, et al.	2005	1,451	226 (16 %)	Menopausal status*
				Stage*
				Number of lymph nodes sampled*
Tanioka, et al.	2010	449	88 (20 %)	Axillary metastases*
				HER2 status*
				Stage
Our study		818	144 (18 %)	Chemotherapy type
				Surgery type
				Race*
				Lymph node status
				Breast cancer side
				Triple-negative status
				Lymph node assessment
				Radiation therapy type

* Statistically significant

significant in predicting recurrence after the achievement of pCR. To our knowledge, our study is the only one to include race in the analysis.

Our study has several limitations. It was performed at a single institution; therefore, the findings may not be generalizable to patients who receive treatment at other institutions, where therapeutic options do not mirror the practices at our institution. This study also only reflects the racial demographics of our institution, most of whom are either African-American or Caucasian, and we could not fully examine breast cancer outcomes in patients of other races. In addition, there may be other unmeasured variables that contribute to an increased risk of recurrence, such as comorbidity. Thus, our exploratory study should be viewed as hypothesis generating for future studies.

In summary, we found that 10.1 % of breast cancer patients who achieved a pCR with neoadjuvant chemotherapy developed local and/or distant recurrence. Patients who were African-American were at higher risk of recurrence after controlling for other clinical and demographic variables. These data emphasize the need for further research to explain reasons why African-Americans with pCR after neoadjuvant chemotherapy are at greater risk of disease recurrence.

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