RESEARCH ARTICLE

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Predictors of Pathological Complete Response to Neoadjuvant Chemotherapy in Iranian Breast Cancer Patients

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Abstract

Background: Achievement of pathologic complete response (pCR) in breast cancer patients receiving neoadjuvant chemotherapy (NAC) is associated with both overall survival and disease-free survival. The aim of present study was to identify clinical and pathological factors associated with achieving pCR in Iranian breast cancer patients receiving NAC. **Methods:** A retrospective review of all breast cancer patients treated with neoadjuvant chemotherapy between April 2012 and September 2016 at our institution was performed; 207 cases were evaluable for analysis. pCR was defined as having no residual invasive tumor in the breast surgical specimen removed following neoadjuvant therapy. **Results:** In univariate analysis, factors associated with pCR were age less than 35 years (p = 0.03), absence of Lymphovascular invasion (LVI) (p = 0.002) and negative hormone receptor status (p = 0.003). Hormone receptor status (P = 0.01; OR, 2.45; CI, 1.20 - 4.99) and LVI (P = 0.001; OR, 0.22; CI, 0.10 - 0.46) remained predictive variables in multivariate analysis after correction for the other variables. **Conclusions:** In conclusion, the results of this study suggests that presence of Lymphovascular invasion and positive hormone receptor status are associated with poorer response to neoadjuvant chemotherapy in breast cancer patients.

Keywords: Breast cancer- pathologic complete response- neoadjuvant chemotherapy

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Introduction

Neoadjuvant chemotherapy (NAC) has become an increasingly popular treatment approach for breast cancer patients. It allows locally advance and inflammatory breast cancer patients become candidate for breast conservative surgery. Moreover, NAC permits assessment of in vivo response to different chemotherapy regimens and making decision regarding subsequent treatments, which could provide an opportunity to switch to a different treatment regimen if disease in an individual patient shows little or no response to the first protocol.

Pathological complete response (pCR) is defined as disappearance of all invasive cancer in the breast after completion of neoadjuvant chemotherapy, although some authors require clearance of residual disease in axillary nodes as well (von Minckwitz et al., 2012). Achievement of pCR has been confirmed to increase both overall survival and disease-free survival with greatest benefits seen in triple-negative and ER-/HER2+ patients (Ferriere et al., 1998; Rody et al., 2007; Symmans et al., 2007; Rastogi et al., 2008; Kong et al., 2011; Cortazar et al., 2014). Hence, in order to identify subset of patients who would most likely benefit from NAC, it is reasonable to detect predictors of pCR in these patients. Despite the well-described role of racial disparity in response to NAC (Li et al., 2003; Chavez-Macgregor et al., 2010; Killelea et al., 2015), the incidence and predictors of pCR among Iranian breast cancer patients have not previously been characterized. The aim of present study was to identify clinical and pathological factors associated with achieving pCR in breast cancer patients receiving NAC at our institution.

Materials and Methods

We conducted a retrospective review of all breast cancer patients treated with neoadjuvant chemotherapy between April 2012 and September 2016 at our institution. Patients with distant metastasis and patients receiving neoadjuvant hormone therapy were excluded.

Study variables included age, menopausal status, histology, T stage, lymph node status, tumor grade, Hormonal receptor status, HER-2 status, Ki 67, Lymphovascular invasion (LVI), type of chemotherapy and pathological response. Initial biopsy specimen of all patients was used to confirm invasive carcinoma. Tumor size was recorded before treatment and was defined as

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the largest dimension on any imaging modality prior to any treatment. Clinical staging was determined based on the American Joint Committee on Cancer TNM Staging Manual, 7th edition. Nodal disease was assessed by physical examination and/or radiological imaging, with or without cytologic diagnosis. ER, PR and HER-2 receptor status was assessed either on the diagnostic core biopsy or on surgical pathology specimen. Hormonal receptor status was considered positive if more than one percent of tumor cells stained for ER and/or PR. Tumors were considered HER2 positive if they were 3+ by immunohistochemistry or demonstrated gene amplification by in situ hybridization. Grade was defined as the highest grade seen on any biopsy.

A pCR was defined as having no residual invasive tumor in the breast surgical specimen removed following neoadjuvant therapy. Patients who had only ductal carcinoma in situ (DCIS) in the breast tissue following neoadjuvant therapy were considered to have a pCR.

For the univariate analyses, Chi-square test or Fisher exact test was used. All variables with a P value < 0.10 in the univariate analysis were included in a logistic regression model and missing data for the predictor variables were handled by multiple imputation. For the multivariate analyses, P values <0.05 were considered statistically significant. All P values were two-tailed. SPSS version 24.0 software (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

From April 2012 to September 2016, 214 patients

Table 1. Characteristics of the Total Population

	All patients, No (%)	pCR, No (%)	No pCR, No (%)	P-value
Age				0.03
<35	45 (27)	21 (31.8)	25 (18.9)	
>35	122 (73)	45 (68.2)	77 (81.1)	
Clinical Tumor Stage				0.21
T1,T2	81 (62.3)	20 (55.6)	81 (62.3)	
T3,T4	49 (37.7)	16 (44.4)	49 (37.7)	
BMI*	28.1 (5.1)	28.3 (5.1)	28 (5.2)	0.84
Menopausal status				0.24
Post	44 (31.9)	13 (27.1)	31 (34.4)	
Pre	94 (68.1)	35 (72.9)	59 (65.6)	
Grade (%)				0.37
Grade 1,2	59 (57.8)	18 (62.1)	41 (56.2)	
Grade 3	43 (42.2)	11 (37.9)	32 (43.8)	
Clinical node status				0.39
Negative	36 (27.7)	13 (30.2)	23 (26.4)	
Positive	94 (72.3)	30 (69.8)	64 (73.6)	
Protocol				
Anthracycline + Taxane	165 (87.8)	54 (84.4)	111 (89.5)	
Other	23 (12.2)	10 (15.5)	13 (10.5)	
Pathology				0.24
IDC	169 (95.5)	54 (93.1)	115 (96.6)	
Non-IDC	8 (4.5)	4 (6.9)	4 (3.4)	
ER/PR				0.003
Positive	92 (45.8)	40 (60.6)	52 (38.5)	
Negative	109 (54.2)	26 (39.4)	83 (61.5)	
Her 2				0.27
Positive	71 (35.5)	21 (31.8)	50 (37.3)	
Negative	129 (64.5)	45 (68.2)	84 (62.7)	
Ki67				
<10%	44 (60.3)	14 (60.9)	30 (60.0)	
>10%	29 (39.7)	9 (39.1)	20 (40.0)	
LVI				0.002
Positive	65 (67.7)	10 (41.7)	55 (76.4)	
Negative	31 (32.3)	14 (58.3)	17 (23.6)	

pCR,Pathologic complete response; BMI, Body Mass Index; LVI, Lymphovascular Invasion; *Mean±SD

Table 2. Multivariate Analysis: Association of Hormone Receptor Status and LVI With pCR

Factors	P value	OR	95% CI
Hormone Receptor Negative	0.01	2.45	1.20 - 4.99
LVI	0.001	0.22	0.10 - 0.46
Age <35	0.26	1.61	0.69 - 3.73

LVI, Lymphovascular invasion; OR, odds ratio; CI, confidence interval

received neoadjuvant chemotherapy at our center. Two patients who received neoadjuvant hormone therapy and five male patients were excluded, leaving 207 cases evaluable for analysis. Clinical and pathological characteristics of the patients differentiated according to pathologic response are shown in Table 1. Overall, 32.9% (68/207) of patients attained a clinical pCR. Patient's median age was 45 years (Range: 20-77). The majority of patients were premenopausal (68.1%). invasive ductal carcinoma was the predominant tumor type (95.5%) and lobular carcinoma consisted only 4.5% of tumors. Regarding the tumor stage, the majority of patients had early stage tumors; 62.3% were T1/T2 and 37.7% were T3/T4. Most of the tumors were hormone receptor (ER and/or PR) negative (54.2%). Her2 over expression was detected in 35.5% of patients. Most of the patients had well diff tumors (57.8%), and LVI was reported in 32.3 percent of cases. The vast majority of patients received Anthracycline/Taxane-based chemotherapy regimens (87.8%) and only 23 patients did not receive either Taxane or Anthracycline as part of their chemotherapy protocol. 34.9% of HER2 positive patients received trastuzumab in combination with their chemotherapy protocol.

In univariate analysis, factors associated with pCR were age less than 35 years ($p = 0.03$), absence of LVI ($p = 0.002$) and negative hormone receptor status ($p = 0.003$) (Table 1).

All factors identified with univariate analyses were entered into a multivariate logistic regression model. Hormone receptor status and LVI remained predictive variables in multivariate analysis after correction for the other variables ($P = 0.01$ and $P = 0.001$ for respectively hormone receptor status and LVI) (Table 2).

Discussion

The current study shows that lymphovascular invasion and ER-PR positivity are significantly associated with unfavorable response to neoadjuvant chemotherapy. To the best of our knowledge, this is the first study that defines pCR rate and evaluates predictors of response to neoadjuvant chemotherapy in Iranian breast cancer patients. 39.2% of patients in our study achieved pCR, which is higher than previous reports (Rastogi et al., 2008; Huober et al., 2010; Liu et al., 2016). This discordant result might be due to higher number of ER-PR negative and younger patients in our study, which is characteristic of Iranian breast cancer patients (Harirchi et al., 2000; Mousavi et al., 2007; Sadjadi et al., 2009).

A negative relation between positive hormone receptor status and pCR has been shown in multiple clinical trial and retrospective studies. In a meta-analysis of 11,695 cases, odds of pCR were highest for the triple negative and HER2 positive/hormone receptor negative subtypes (Houssami et al., 2012). Conversely, another recent meta-analysis of 9,460 cases from 27 studies reported higher pCR rate in triple negative patients compared with non-triple negatives (Wu et al., 2014). In this study, hormone receptor negative patients three times more likely achieved complete response compared with hormone positive patients, which is in line with previous researches (Ring et al., 2004; Tan et al., 2009; Huober et al., 2010; Liu et al., 2016). These results fortify the existing data that ER/PR positive tumors are generally resistant to chemotherapy, and that alternative approaches of treatment should be considered for these tumor subtype.

The results of our study are similar to prior studies of LVI in breast cancer patients receiving neoadjuvant chemotherapy. Uematsu et al reported LVI as an important factor in predicting NAC efficacy for breast cancer (Uematsu et al., 2011). In a retrospective study of 388 patients treated with anthracycline-based NAC, Keskin et al also found LVI to be significantly associated with chemoresistant breast cancer (Keskin et al., 2011). More recently, another study by Abdel-fatah et al suggested that LVI was a significant factor that predict response and survival in patients receiving NAC (Abdel-Fatah et al., 2015).

The current study also showed that younger patients more likely achieve pCR, although this difference was not observed when a higher cutoff for age was selected (50 years; data not shown). Our results are in accord with previous studies; In the GeparTrio study, Age less than 40 years was significantly associated with the achievement of mid-course response as well as a pCR (Huober et al., 2010). More recently, in another study of 8,949 women with operable or locally advanced breast cancer who were treated with neoadjuvant chemotherapy, age was an independent predictive factor for pathologic complete response, Disease-free survival and local recurrence-free survival (Loibl et al., 2015).

Numerous studies have assessed the role of HER2 in predicting the response to neoadjuvant chemotherapy with conflicting conclusions (Bozzetti et al., 2006; Tan et al., 2009; Houssami et al., 2012; Babyshkina et al., 2014; Tanioka et al., 2014; Nwaogu et al., 2015). The inconsistency of the data found in these reports might be due to incorporation of HER2-directed therapy with NAC in more recent studies. Indeed the available data suggest that HER2 overexpression is regarded as a positive predictive for pCR only for patients who receive trastuzumab as part of their neoadjuvant chemotherapy

regimen (Houssami et al., 2012). Although a higher number of pCR rate was observed in patients treated with anti-HER2 directed therapy, we did not detect a relationship between HER2 overexpression and pCR rate in this study, mainly due to high number of HER2 positive patients who did not receive trastuzumab treatment. Still, when patients treated with neoadjuvant chemotherapy combined with anti-HER2 therapy were analyzed, a higher pCR rate was observed.

Although several study have reported higher pCR rate with smaller clinical tumor size, we did not find such correlation in this study. This could be explained by the dramatic difference of tumor size in our study compared with others. While most of the patients in other studies had advanced tumors (Huober et al., 2010; Keskin et al., 2011), T1/T2 lesions were predominant in current study (62%).

This study has some limitations. First, due to retrospective nature of this study, causality is not possible to assess and we could only show association. Additionally, as with all retrospective studies, results of this study are prone to patient and treatment selection bias. Second, not all patients with HER-2-positive disease in our study received trastuzumab as part of their treatment. Acknowledging these limitations, the present study suggests that presence of LVI and positive hormone receptor status are associated with poorer response to neoadjuvant chemotherapy in breast cancer patients.

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