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Research Article

Impact of Breast Cancer Subtypes on Pathological Complete Response Following Neoadjuvant Chemotherapy

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Abstract

Objectives: We aimed to identify the clinicopathological characteristics associated with pathological complete response (pCR) following neoadjuvant chemotherapy in breast cancer.

Methods: Between 2009 and 2020, 105 female patients diagnosed with non-metastatic, T1-4, N1-3 breast cancer, undergoing neoadjuvant therapy followed by surgery and then radiotherapy were included in the study. All patients received anthracycline and taxane-based treatments. Patients with Her-2 positivity received additional trastuzumab treatment.

Results: A total of 105 female patients were included in the study. The median age was found to be 52 years. 50 (47.6%) patients were premenopausal and 55 (52.4%) patients were postmenopausal. Pathological complete response was obtained in 26 (24.7%) patients who received neoadjuvant therapy. In the evaluation of the factors affecting the pathological complete response, statistical significance was obtained in progesterone receptor status and breast cancer subtypes in the multivariate analysis ($p<0.003$, $p<0.035$, respectively).

Conclusion: This study showed that the pCR rate was considerably higher in patients with triple negative subtype compared to those with other breast cancer subtypes.

Keywords: Breast cancer, neoadjuvant theraphy, pathological complete response

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Breast cancer is the most common malignant tumor in women and the most common cause of mortality. Although breast cancer-related mortality rates have decreased recently with great advances in cancer treatment, breast cancer is still one of the leading causes of death among women today.[1]

The frequency of use of neoadjuvant therapy in inflammatory and high-risk localized breast cancer is increasing in today's practice. Although no difference was found in terms of survival in local stage breast cancers treated with adjuvant or neoadjuvant treatment, it is important in terms of facilitating breast conserving surgery and monitoring the response during treatment.[2,3]

Evaluating the intrinsic molecular subtypes of breast cancer is important because it has prognostic value. It can be divided into 4 groups according to the expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth receptor 2 (HER-2) and Ki-67. Luminal A subtype involves ER/PR+, HER-2 – and Ki-67 <20 tumors; Luminal B subtype involves ER/PR+ and Ki-67>20 tumors, HER-2 + subtype involves ER/PR- and Her-2 positive tumors and triple negative (TN) subtype involves ER/PR–HER2– tumors.[4,5]

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Pathological complete response (pCR), has been shown to be a surrogate marker for disease-free survival (DFS), and overall survival (OS) after neoadjuvant therapy. While pCR was associated with improved long-term outcomes for HER2 positive breast cancer and triple negative (TN) breast cancer, pCR rates were lower in the hormone receptor positive (HR+)/HER2 group.[6]

In our study, we planned to investigate the factors affecting the pathological complete response in patients with local stage breast cancer who received neoadjuvant therapy.

Methods

105 patients diagnosed with breast cancer between 2009-2020 at the University of Health Sciences Umraniye Training and Research Hospital were included in the study. The study was performed according to the institutional ethical standards (University of Health Sciences, Umraniye Training and Research Hospital, Number: B.10.1.TKH.4.34.H.GP.0.01/45). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Inclusion criteria: female patients diagnosed with non-metastatic , T1-4, N 1-3 breast cancer, undergoing neoadjuvant therapy followed by surgery and then radiotherapy

Tumor biology was categorized into 4 groups. Luminal A: ER/PR+, HER-2 – and Ki-67 <20, Luminal B: ER/PR+ and Ki-67>20, HER-2 + group, triple negative (TN) group: ER/PR–HER2–. The cut off values for estrogen receptor (ER) and progesterone receptor (PR) were ≥1% positive nuclei. HER2 was collected at diagnosis for all patients at our institution using standard immunohistochemistry, as well as fluorescence in situ hybridization when indicated. Ki-67 score is defined as the percentage of positively stained cells among the total number of malignant cells scored. All patients received anthracycline and taxane-based treatments. Patients with Her-2 positivity received additional trastuzumab treatment.

Statistical Analysis

Descriptive statistics and chi-square test were used to evaluate the frequencies and comparison between pCR and non-pCR groups. pCR was defined as no residual invasive disease in the breast and axilla, with noninvasive residuals permitted, including ductal carcinoma in situ (ypT0/is ypN0). Univariate and multivariate Cox Regression Model were used to identify the prognostic factors for pCR. Overall survival (OS) was defined as the time from the first pathological diagnosis to death, and disease-free survival (DFS) as the time from diagnosis to progression/relapse or death. All statistical analyses were performed by SPSS 17.0 software and p value<0.05 was considered as statistically significant.

Results

A total of 105 female patients were included in the study. The median age was found to be 52 years. Fifty patients (47.6%) were premenopausal and 55 (52.4%) patients were postmenopausal. When patients are evaluated according to breast cancer subtypes; 15 (14.3%) patients were in the luminal A group, 33 (31.4%) patients were in the luminal B group, 37 (35.2%) patients were in the Her-2 positive group, and 20 (19.1%) patients were in the triple negative group. Pathology of 72 (68.5%) patients consisted of invasive ductal carcinoma. Tumors of 104 (99%) patients consisted of grade 2-3. Lymphovascular invasion was detected in 26 (24.7%) patients, and perineural invasion was found in 20 (19%) patients. Pathological complete response was obtained in 26 (24.7%) patients who received neoadjuvant therapy. The clinicopathological features according to pCR satatus were presented in Table 1. In the evaluation of the factors affecting the pathological complete response, statistical significance was obtained in progesterone receptor status (p<0.003) and breast cancer subtypes (p<0.035) in the multivariate analysis (Table 2). Median OS and DFS could not be reached due to insufficient number of events.

Discussion

There are several reasons to use neoadjuvant chemotherapy in breast cancer, some of which are to improve breast conservation (either with downstaging or with conversion of tumors from inoperable to operable state), assess treatment response, give time to analyze tumor samples for further molecular tests. However among all, the most important goal of preoperative chemotherapy in breast cancer is to improve outcome through providing complete pathologic response. In this study assessing the effect of breast cancer subtypes on response to neoadjuvant chemotherapy and predicting outcome, the subtypes of breast cancer were found to have impact on pCR.

The response to neoadjuvant chemotherapy differs among major subtypes of breast cancer. The best response is seen in triple-negatif breast cancer followed by Her-2 positive subtype. Because these subtypes include high expression of proliferation genes, they are specifically vulnerable to cytotoxic chemotherapy.[7-9] In a meta-analysis including 11695 patients to evaluate association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy, odds of pCR were highest for the triple negative and HER2+/HR- subtypes.[10] In our study we found that pCR was obtained in 50% of triple-negative subtype which was the highest ratio among all subtypes. Triple-negative subtype was followed by Her-2 positive, Luminal A and Luminal B subtypes with corresponding pCR rates of 35.1%, 6.6% and 6%.

Table 1. Demographics, and clinical characteristics of patients

	All patients, n (%) n=105	pCR, n(%) n=26 (24.7)	No pCR, n (%) n=79 (75.3)	p
Age, median	52	51.5	52	0.737
Luminal A	15 (14.3)	1 (6.6)	14 (93.4)	<0.001
Luminal B	33 (31.4)	2 (6)	31 (94)	
HER-2 positive	37 (35.2)	13 (35.1)	24 (64.9)	
Triple negative	20 (19.1)	10 (50)	10 (50)	
T1,T2	96 (91.4)	24 (25)	72 (75)	0.268
T3,T4	9 (8.6)	2 (22.2)	7 (77.8)	
N1	32 (30.4)	8 (25)	24 (75)	0.320
N2	73 (69.6)	18 (24.6)	55 (75.4)	
Grade				
1	1 (1)		1 (100)	0.317
2	64 (61)	13 (20.3)	51 (79.7)	
3	40 (38)	13 (32.5)	27 (67.5)	
Menopausal status				
Pre	50 (47.6)	12 (24)	38 (76)	0.522
Post	55 (52.4)	14 (25.4)	41 (74.6)	
Ki-67				
<20	23 (21.9)	3 (13)	20 (87)	0.215
>20	82 (78.1)	23 (28)	59 (72)	
LVI				
Yes	26 (24.7)	7 (26.9)	19 (73.1)	0.478
No	79 (75.3)	19 (24)	60(76)	
PNI				
Yes	20 (19)	5 (25)	15 (75)	0.591
No	85 (81)	21 (24.7)	64 (75.3)	

pCR: Pathological complete response; HER-2: Human epidermal growth receptor 2; LVI: Lymphovascular invasion; PNI: Perineural invasion

Carey et. al. in their research, examined both the response patterns of breast cancer subtypes to neoadjuvant chemotherapy and the impact of response on distant disease-free survival.[11] Complete pathologic response was observed in 7% of luminal subtypes, 27% of basal-like and 36% of HER2+/ER- subtype. Pathologic complete response was closely coupled with good prognosis regardless of the breast cancer subtype in the entire cohort. Distant disease-free survival was shorter among basal-like and HER2+/ER- subtypes with residual disease after chemotherapy compared with luminal subtypes. We, in the present study did not perform gene expression analysis to identify intrinsic breast cancer subtypes and due to the insufficient number of events, survival outcomes could not be estimated.

In the trial conducted by Prat et al.,[12] pathologic response and survival was evaluated according to the intrinsic breast cancer subtypes following neoadjuvant chemotherapy. The authors reported that the molecular subtypes were independently associated with pCR in the multivariable analysis, after adjusting age, tumor size, grade and ER, PR and HER-2 statuses. Furthermore, within patients that did not achieve a pCR, intrinsic subtype was found to be significantly associated with distant relapse-free survival in both univariate and multivariate analyses. However among those that achieved a pCR, no clinicopathological or molecular variable was found to be significantly associated with distant relapse-free survival. In the current study, according to the results of multivariate analysis, progesterone receptor negativity and triple-neg-

Table 2. Univariate and multivariate analysis of potential factors associated with pCR

	Univariate analysis, p	Multivariate analysis, p
PR status	0.001	0.003
ER status	0.003	
Subtypes (Luminal A, Luminal B, HER-2 positive, triple negative)	0.001	0.035

pCR: Pathological complete response; PR: Progesteron receptor; ER: Estrogen receptor; HER-2: Human epidermal growth receptor 2

ative breast cancer subtype were identified as features that independently predict pCR.

We only performed pathology-based subtype classification in the present study. It is one of the potential weaknesses of this research. If a gene expression-based analysis had been done, a different gene signature might be identified. Having a retrospective design hence a predisposition to selection bias is an another limitation of the study. Lastly, small sample size may preclude further significance of statistical findings such as survival times.

In conclusion, the findings of the present work confirms that pCR rates were considerably higher in triple negative and Her-2 positive breast cancer subtypes compared to Luminal subtypes. In real life practice, gene expression profiles are infrequently used due to diffuculties in accessibility. Thus, our study investigating the response patterns to neoadjuvant chemotherapy and outcomes in breast cancer patients with pathological-based classification of subtypes adds real -world experience to the existing literature.

Disclosures

Ethics Committee Approval: The study was approved by The University of Health Sciences, Umraniye Training and Research Hospital Ethics Committee (Date: 10/02/2022, No: B.10.1.TKH.4.34.H.GP.0.01/45).

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