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Pathological Factors Predicting Neoadjuvant Chemotherapy Response and Survival in Breast Cancer

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Abstract

Purpose: In the case of developing resistance to systemic neoadjuvant chemotherapy, patients might tend to present with more advanced diseases later on and become inoperable at the end of their course. We have tried to determine the predictive factors for complete pathological response.

Materials and Methods: Records of 115 patients were reviewed retrospectively. We have collected data related to patient's sociodemographic features, disease free survival and overall survival, as well as the clinical, histological, molecular and pathological features of their tumor. We have used SPSS statistic program (SPSS 20.0, SPSS Inc. Chicago, Illinois) to analyze statistical inputs.

Findings: 26 patients (22.6%) showed pathological Miller Payne Grade 5 response (T0) and 3 patients showed no measurable tumor, residue with separate tumor cells (T1mi). Presence of *HER2-neu* expression (p: 0.03), absence of ER and PR expression (p=0.001) and high histological grade (p: 0.025) were found to be associated with complete pathological response. Tumor diameter and lymphoid infiltration were not correlated with complete response. Also, we found that, patients who showed lower pathological nodal stage according to AJCC 8th system, have statistically significant longer survival times (p<0.05 for all), but Miller-Payne Grade 5 response were not predict survival results (p: 0.814 for OS) (p=0.295 for PFS).

Conclusion: Neoadjuvant treatment would be more effective in these types of tumors. Survival effect can be better predicted with pathologic nodal results according to AJCC 8th system. There is a need for randomized prospective studies so that the treatment response can be assessed more appropriately.

Keywords: Breast cancer; Neoadjuvant; Chemotherapy; Survival

Introduction

Breast cancer is one of the three most common cancers along with lung and colon cancer. It is a leading cause of cancer deaths in both developing and developed countries. Even though mortality from breast cancer has decreased under favor of early detection and efficient therapies especially in the US and Europe, it is still a serious problem worldwide [1]. Therapy of the breast cancer has progressed over the years both for regional and systemic therapeutic options. Other than surgical resection, depending on locoregional tumor load, histopathological characteristics and molecular subtypes; therapeutic backbone involves chemotherapy, anti-HER2 targeting and hormonal therapy.

Neoadjuvant chemotherapy (NAC) could eliminate potential micrometastatic focuses existed and prevent growth of occult micrometastases that originated from released tumor cells during surgery [2]. Additionally, NAC allows breast conserving in higher rates and can be used as an assessment for tumor sensitivity to chemotherapy. Whereas main expected benefit of treatment modalities is to improve disease-free and progression-free survival, investigators are trying to translate therapy results into survival rates. While aiming best survival results, avoiding under-treatment or overtreatment is critical and determining the extent of the therapy is still an issue. Because of the pathological examination has decision-making importance and even though it has not been universally standardized. Breast cancer has been staged using the AJCC Tumor, Node, and Metastasis (TNM) staging system since the 1st edition cancer staging system in 1977 based on anatomic factors. TNM staging system revised in 2018, and now includes anatomic stage groups as well as two prognostic stage groups, a pathologic and a clinical prognostic stage group [3]. There are many other different neoadjuvant response evaluation systems and "Miller-Payne Criteria" is accepted useful in various cancer centers, which has grades from 1 to 5 gradually [4]. However, clinical course of patients with pCR is not yet clear due to conflicted results.

Could cPR be surrogate marker for survival outcomes? We aimed with this study to investigate the factors that predict response to neoadjuvant therapy, and to assess correlation between pathological responses and survival rates.

Materials and Methods

Patients

A total of 137 breast cancer patients who were admitted to Medical Oncology Outpatient Clinic of Istanbul University Cerrahpasa Medical Faculty Hospital between January 1, 2011 and December 31, 2015 in order to receive neoadjuvant chemotherapy were included in the

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present study. Socio-demographic characteristics, location of tumor, grade and stage of tumor, histological and pathological features of the tumor, molecular markers of the tumors, treatments, length of disease-free time and overall survival time were determined retrospectively from patient files.

Clinic records of patients were retrospectively scanned, patients' latest statue were updated and then included in the study. Patients who could not be contacted, those whose pathological information could not be determined, and patients initially planned to receive neoadjuvant therapy but were not operated for different reasons were not included in the study. In addition, patients who initially admitted to our hospital but continued treatment in other hospitals were also excluded. Thus, 22 patients were excluded and a total of 115 patients were included in the study. Ethical approval of the study was obtained from Cerrahpasa Medical Faculty Ethics Committee Commission (Date: 02.02.2016, Number: 83045809/604.01/02-44109).

Clinical and pathological evaluation

Variables such as age, sex, menopausal status, history of birth, family history of cancer, tobacco and alcohol use, and secondary disease information at the time of diagnosis of the patients included in the study. Ultrasonography, magnetic resonance imaging or PET-CT imaging was used to define tumor size and localization at the time of diagnosis. The criteria for the diagnosis of inflammatory breast carcinoma were determined by the clinical oncologist evaluation as recommended by AJCC 8th. The patients were divided into two groups according to their imaging of axillary involvement and pathological findings. The staging was performed according to AJCC 8th criteria.

In the evaluation of estrogen and progesterone receptor expression, cell nuclei staining of 1% or more was considered positive in immunohistochemical staining. HER-2neu expression was accepted as negative in patients with Score 0 and Score 1 and positive in patients with score 3 according to membrane positivity ratio in immunohistochemistry staining. *In situ* hybridization of HER-2neu gene expiration was requested from all patients with score 2 to determine the positive or negative status.

Treatment regimens were mostly anthracycline and taxane-containing regimens, all patients with HER-2neu expression were given Trastuzumab along with taxane therapy. Patients with inadequate response to clinical evaluation underwent chemotherapy or radiotherapy according to the clinician's choice. After the operation, adjuvant radiotherapy or chemotherapy was planned based on the current guidelines and according to the pathological and clinical features. One-year adjuvant Trastuzumab treatment was planned in all HER-2neu positive patients and adjuvant hormone therapy was planned in patients with any positive rate of hormone receptor.

Evaluation of treatment response was based on tumoral involvement in the pathological material of breast or lymph nodes. Patients were grouped according to Miller-Payne Score in pathological response evaluations. Surgical and pathological staging was performed in accordance with AJCC 8th criteria.

Statistical analysis

For the survival analysis, last evaluation date of March 2019 assured for the examination of the patients. All patients with no communication for a longer period of time were contacted by telephone and the latest statue was updated. Overall survival time was recorded as the length of time between the date of surgery and the date of death or last follow-up. Disease-free survival time was recorded in an analogous manner by calculating the time between surgery and the date of confirmed disease recurrence or death.

Microsoft Excel 2010 and SPSS statistical analyses software program (SPSS 20.0, SPSS Inc. Chicago, Illinois) were used for data handling and statistical analysis. The Kaplan-Meier method was used for disease-free and overall survival time analysis and log-rank regression analysis was used to determine the relationship between prognostic factors and survival. P-value of 0.05 or less was considered as the statistical significance. The factors that might affect the pathologic complete response were evaluated by the Chi-square test.

Results

Patients

The mean age of the patients was 49 years (Range: 23 years to 77 years). Two of the patients were male and three were pregnant at the time of diagnosis. Hypertension was the most common comorbid disease. The sociodemographic data of the patients are summarized in Table 1. The mean tumor size was 4.02 cm (range 1 to 13.8 cm) and invasive ductal carcinoma was the most common histology (80.8% of 93 patients). Multifocal tumors were detected in 16 (13.9%) and multicentric tumors in 21 (18.2%) patients. Each of the 4 patients with bilateral tumors was evaluated as two separate tumors for pathological response. There were 109 patients with nod positive disease at the beginning. The histopathological features of the patients are shown in Table 2.

Most of the patients were treated with anthracycline and taxane as a standard neoadjuvant treatment regimen. Dose modifications were performed in 4 patients due to side effects and two patients received neoadjuvant hormone therapy for increased age. Neoadjuvant radiotherapy was given to two patients due to insufficient response. Also additional chemotherapy treatments with gemcitabine were planned for these patients. 5 patients were initially oligometastatic and went to surgery after response evaluation.

In the post-operative evaluation, the mean tumor size was 2.25 cm (Range 0.1 cm to 13 cm). No measurable tumor was detected in 29 patients (24.4%). In three of these, a few tumor cells were observed on the background of fibrotic tissue (T1mi). The number of patients with ypN0 on pathological nodal evaluation was 45 (39.1%). Neoadjuvant response according to Miller-Payne Scoring were classified as, Grad-5 for 26 patients (21.8%), Grad-4 for 11 patients (9.2%), Grad-3 for 19 patients (16%), Grad-2 for 33 patients (27.7%) and Grad-1 for 18 patients (15.1%). Two of the 5 metastatic patients had MPS Grade 5 response, that confirming also clinical regression seen before surgery.

When patients with MPS Grade 5 response were evaluated among themselves; all patients were female. A total of 10 patients (38.5%) had inflammatory breast carcinoma. In the follow-up, 4 patients had distant metastasis after treatment. The tumor stage before treatment were T1 for 2 patients (7.7%), T2 for 12 patients (46.2%), T3 for 2 patients (7.7%) and T4 for 10 patients (38.5%). Except one patient, all the patients were radiologically node positive. ER expression was detected in 8 patients, of which only 4 were associated with PR. 17 patients were HER 2 positive, 2 of them were score 2 and confirmed by FISH. In the lymph node staging of the patients after surgery; one had pN1 and three had pN2.

Recurrence and survival results

Survival analysis did not include patients with metastatic disease

Characteristics		n=115
Age	Median	49
	Range	23-77
Gender	Male	2 (1.8%)
	Female	113 (98.2%)
Menopausal Status	Post	41 (42.7%)
	Pre	52 (54.2%)
	Peri	3 (3.1%)
Smoking history	<10 packages/year	3 (4%)
	>10 packages/year	13 (16.6%)
	No	62 (79.4%)
Parity	Nulliparous	9 (17.3%)
	Primiparous	10 (19.23%)
	Multiparous	33 (63.47%)
Family Cancer History	**First Degree**	
	Breast	6 (7%)
	Other	28 (32.9%)
	Second Degree	
	Breast	12 (14.1%)
	Other	14 (16.5%)
Other Disease History	Hypertension	21 (18.5%)
	Diabetes	10 (11.7%)
	MI, KKY	2 (1.76%)
	Tetralogy of Fallot	1
	Factor 11 deficiency	1
	Other Cancer	4

Table 1: Socio-demographic data of patients.

T stage, n=119*	T1	10 (8.5%)
	T2	44 (37.3%)
	T3	6 (5.1%)
	T4	58 (49.2%)
Nodal Status, n=115	Negative	2 (1.7%)
	Positive	109 (94.8%)
	Unknown	4 (3.5%)
Localization n=115	Right Breast	65 (56.5%)
	Left Breast	46 (40%)
	Bilateral	4 (3.5%)
Grade, n=119*	Grade 1	-
	Grade 2	56 (47.1%)
	Grade 3	34 (28.6%)
	Unknown	29
Characteristic, n=115	Multifocality	18 (15.7%)
	Multicentrisity	22 (19.1%)
	Inflammatory tumor	56 (48.7%)
ER status, n=119*	Positive	68 (61.8%)
	Negative	42 (38.2%)
	Unknown	9
PR status, n=119*	Positive	55 (50%)
	Negative	55 (50%)
	Unknown	9
HER2-neu status, n=119*	Positive	38 (34.5%)
	Negative	72 (65.5%)
	Unknown	9
*Four bilateral tumors were considered as two separate tumors in the classification of tumoral features.		

Table 2: Distribution of patients according to pre-treatment tumor characteristics.

from the beginning. Four of these patients were still alive at the time of analysis. Disease recurrence was detected in 38 patients (33%), four of whom had local recurrences and others had distant metastasis. When a patient with primary unresponsive was excluded, the earliest relapse was detected within 2 months and at the latest after 80 months. Of the patients with recurrence, only 4 patients had a Grade 5 treatment response score and they had distant metastasis.

At the median follow-up time with 50.3 months, the 5-year disease-free survival rate of all patients was 64.1% ± 4.8. At the median follow-up with 54.5 months, overall survival rate was 75.2% ± 4.5 for all cohorts. Age, menopausal status and tumoral ER-PR-HER2 status, Grade or inflammatory character did not show significant effect in survival analysis. Postoperative pathologic nodal staging were associated with 5-year DFS and OS. Although numerically improved survival was observed, patients with Miller-Payne response grade 5 have not statistically significant different survival results compared with others (Table 3). Data also were evaluated with chi-square test in terms of factors that may affect the pathological complete response of the tumor. High tumor grade, negative hormone receptors, and HER2 positivity were statistically significant (Table 4).

Discussion

Neoadjuvant chemotherapy provides possibility for a successful surgical operation by reducing tumor size in locally advanced breast carcinoma and allows breast conserving surgery. Micrometastatic disease is assumed to be present at the time of diagnosis in patients with locally advanced breast cancer [5]. With neoadjuvant therapy, it is also aimed to prevent the progression of these micrometastatic foci after surgery. Nevertheless, complete response rates after Neoadjuvant therapy remains between 20% to 30% [6] and nearly 20% of patients may not respond to chemotherapy [7]. These patients are exposed to

Variables	5-years PFS	p-value	5-years OS	p-value
Miller-Payne Grade				
Grade 1 (n: 18)	53.3% ± 12.9%	0.295	68.2% ± 11.8%	0.814
Grade 2 (n: 33)	72.7% ± 8.3%		76.9% ± 8.7%	
Grade 3 (n: 19)	58.2% ± 12.1%		81.4% ± 9.7%	
Grade 4 (n: 11)	60% ± 15.5%		80% ± 12.6%	
Grade 5 (n: 26)	79.2% ± 9.6%		85% ± 8%	
Pathologic Nodal Stage				
pN0 (n: 45)	71.6% ± 7.3%	0.02	82.9% ± 6.6%	0.01
pN1 (n: 25)	69.6% ± 9.6%		81.3% ± 8.7%	
pN2 (n: 31)	61.9% ± 9.6%		75.9% ± 8.8%	
pN3 (n: 17)	35.7% ± 12.8%		40.2% ± 13.6%	

Table 3: Post-operative pathological response characteristics and survival results.

Variables	p-value
Menopausal Status	0.527
Tumor Placement	0.494
Inflammatory Properties	0.315
Multifocality	0.963
Multicentricity	0.757
Histological subtype	0.964
High Grade	0.025
ER negativity	0.001
PR negativity	0.001
HER2-neu positivity	0.03

Table 4: Factors predicting complete response.

unnecessary chemotherapeutic toxicity with ineffective treatment and miss the chance of early surgery. Therefore, there is a need for new methods to determine the tumor characteristics before treatment. In addition, predicting the group that does not respond well in advance will motivate clinicians to develop new chemotherapy regimens or medications that can be given to these patients (Figure 1).

The definition of pathological complete response varies in publications. In some studies, the absence of tumor cells in breast tissue was defined as a complete response [8,9], whereas the absence of tumors in both breast and axillary lymph nodes was considered as a complete response in others [10]. We evaluated the response either according to the AJCC 8th and Miller-Payne scores as a comparable factor in our pathology unit. AJCC TNM 8th Edition defines pathological complete response as no tumor cell on breast and nodal specimens, pN0 has no tumor cell on lymph node [3]. In Miller-Payne (MP) grading system, Grade 1-4 are categorized as partial pathological response (pPR) and grade 5 as pathological complete response (pCR) (4). In this study, Miller–Payne Grade 5 responses were found in 26 cases (22.6%). This is similar to the rates found in other publications [11,12].

There are studies that report the absence of a relationship between age and response [13]. Whereas some publications suggested an inverse relationship, a statistically significant complete response rate of up to 37% over the age of 50 was reported earlier [14]. Some publications emphasized that tumors with high proliferative features are more common in younger ages and neoadjuvant response is better in young patients [15]. Since menstruation status is usually related to age, it is difficult to evaluate it independently. In most studies, no evidence was found to predict treatment response. Age and menopausal status of our patients also was not a factor affecting the pathological response.

Hormone receptor positivity is a strong predictor of response to endocrine therapy. In particular, the benefits of adjuvant therapy are indisputable. When the relationship between hormone receptor positivity and neoadjuvant chemotherapy response is examined, an

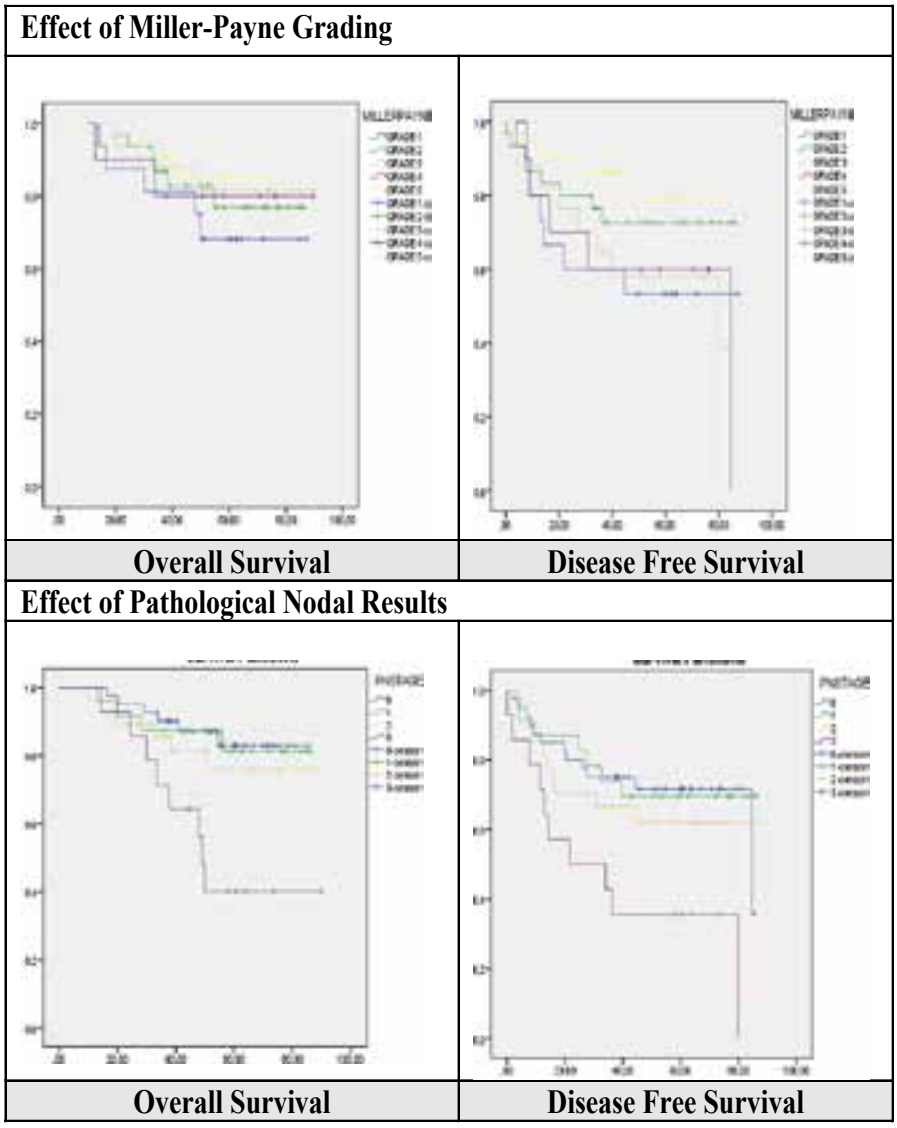

Figure 1: Survival results of patients.

inverse relationship was evident. It is known that in the case of positive hormone receptor, the Luminal group tumors have low response to chemotherapy [16]. In many studies examining neoadjuvant treatment responses, ER status was evaluated as a determinant marker of chemosensitivity, and it was shown that ER negativity could predict treatment response [12,17,18]. In the 'European Cooperative Trial in Operable Breast Cancer' (ECTO-2) study, 1355 patients were evaluated and 45% of ER negative patients showed pathological complete response. In the ER positive group, the response remained about 10%. In multivariate analysis, ER status was the only significant independent variable in the study [19]. In another study, ER negativity was closely associated with a high histological grade and it was observed that ER negative tumors responded significantly better, even if they were grade-dependent [20]. Similarly, we found that ER negativity and PR negativity were statistically significant factors affecting the development of pathological complete response. In all these studies, it was also emphasized that despite complete response to ER negative tumors, disease-free survival rates were significantly lower than ER-positive tumors. This may be attributed to the idea that ER negativity leads to more aggressive tumor growth. In contrast, there have also been studies that did not detect an association between negative ER expression and anthracycline-based chemotherapy response [21]. In particular, studies evaluating the small number of patients could not demonstrate this association [22,23].

The *HER2-neu* gene was reported to be positive in approximately 30% of breast cancers [16]. *HER2-neu* was found to be positive in 36.7% of our patients during the pre-treatment evaluations. The relationship between *HER2-neu* expression and chemotherapy response is controversial. Increased expression of HER2 is associated with resistance to docetaxel treatment *in vitro*, and trastuzumab treatment is thought to sensitize breast cancer cells to docetaxel [24]. Conversely, it is argued that HER2 positivity increases the anthracycline susceptibility of the tumor, due to the increase of topoisomerase 2 expressions on chromosome 17 or the presence of polysomy on chromosome 17. HER2-positive tumors with topoisomerase 2 amplification were more sensitive to anthracycline [25]. Moreover, in a study evaluating triple negative patients, patients with *HER2-neu* score of 2 were examined separately and they were reported to be more chemo-sensitive than the negative group, albeit not being able to predict the pathological complete response [26]. In a study, patients who received neoadjuvant chemotherapy with anthracycline and paclitaxel were examined. Even trastuzumab was not administered in HER2 positive patients, pathological complete response rates were 75% in ER negative group and 50% in ER positive group. When these results were compared with the data of HER2-negative patients, HER2 positivity was found to be an independent predictive factor [27]. In a separate study, pathological complete response rate was found to be high in patients with ER negativity, HER2 positivity, and high nuclear grade, but HER2 positivity did not appeared as independent predictor in multivariate analysis [12]. Moreover, in a study evaluating triple negative patients, patients with *HER2-neu* score of 2 were examined separately and they were reported to be more chemosensitive than the negative group, albeit not being able to predict the pathological complete response [26].

Tumors with high histological grade tend to be more aggressive. However, due to the high cell division rates, it is thought that cells are more likely to respond to chemotherapy during the division phase, which is more sensitive to treatment. Supporting this hypothesis, there are findings suggesting that tumors with high histologic grade may predict the pathological complete response in anthracycline-containing neoadjuvant therapy [12,21,22].

Similar to previous studies, it was also found that hormone receptor negativity, *HER2-neu* positivity and higher grade were statistically significant factors affecting pathological complete response development.

Evaluating chemotherapy response is essential to predict survival rate and guide future chemotherapy. Although there are few studies with contradicting results [21], survival was significantly prolonged in patients with pathological complete response after neoadjuvant chemotherapy than those without response [28,29]. In the NASBP-18 study that evaluated approximately 1500 patients, both disease-free survival and total survival were significantly longer in patients who received clinical and pathological complete response after 9 years of follow-up [9].

Until now, the evaluation of pathological response mainly involves quantitative assessment and is often inconsistent with clinical response. There are different systems to evaluate the pathological responses other than Miller-Payne (MP), such as the systems of Chevallier, NSABP B-18, Pinder, Sataloff and Smith [9,30,31]. However, the efficacy of these methods to predict outcomes remains preliminary. Different classification systems were compared with each other within some other studies, and results showed that, pathological systems which consist also lymph node response better predicts survival [32,33].

We therefore evaluated correlation of survival and pathological nodal status and showed a statistically significant relation. Based on these results, TNM results are seems to better predict survival after neoadjuvant treatment.

Conclusion

In conclusion, our retrospective study showed that negative ER and PR receptors, high tumor grade, and HER2 positivity are the determinants of the pathological complete response obtained by chemotherapy regimens. Also survival is better predicted with pathologic nodal staging rather than Miller-Payne Scoring system. At the moment, there is no standard method to assess the pathological response to primary chemotherapy in patients with LABC. Hence, the standardization and improvement of methods to assess the response to induction chemotherapy are sorely needed. Randomized prospective studies are needed to select a more balanced choice of patient characteristics and treatment schemes at the beginning and to evaluate the treatment response more appropriately.

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