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Original Research

Real-Life Data of Neoadjuvant Chemotherapy in Breast Cancer: Aegean Region Experience

Atike Pınar Erdoğan[1], Ferhat Ekinci[2], Ahmet Özveren[3], Emine Bihter Eniseler[1], Bilgin Demir[4], Mustafa Şahbazlar[1]

[1] Department of Internal Medicine Divison of Medical Oncology, Manisa Celal Bayar University, Medical Faculty, Manisa, Turkey

[2] Medical Oncology Clinic, Şırnak State Hospital, Şırnak, Turkey

[3] Kent Hospital Oncology Center, İzmir, Turkey

[4] Medical Oncology Clinic, Atatürk State Hospital, Aydın, Turkey

ABSTRACT

Objective: The use of neoadjuvant chemotherapy (NACT) in breast cancer is increasing. However the management of locally advanced breast cancer differs due to the approach of the center to which the patient applied and the approach of the following physician. From this point of view, we aimed to evaluate the real life data of our region.

Methods: The study included 106 patients treated with NACT in the medical oncology clinic of two different university hospitals. Association between clinicopathological features and pathological complete response (pCR) were analyzed.

Results: The pCR rate was higher in patients with negative hormone receptors and this difference was statistically significant (p:0.000). The rate of obtaining pCR increased as the NACT duration increased, and this increase was statistically significant. The mean NACT duration applied to the patients with pCR was 5.48 ± 0.22 months, and the mean NACT duration for those who could not obtain pCR was 5.01 ± 0.1 months (p:0.041). The recurrence rate of patients with pCR was 11.1%, while the recurrence rate of patients who could not obtain pCR was 31.6% (p:0.04).

Conclusion: Pathological response to chemotherapy is an important factor in determining prognosis. There appears to be a need for new biomarkers that allow the prediction of pCR and long-term outcomes.

Keywords: breast neoplasms, developing countries, neoadjuvant therapy, pathologic response

INTRODUCTION

Breast cancer is the most common cancer in women worldwide and is the leading cause of cancer-related death in women [1]. 80-85 % of the patients have local disease, 15% have locally advanced disease, and 5% have clinically evident metastatic disease [2]. Since locally advanced breast cancer is a highly heterogeneous group, disease management and treatment responses also vary. At this point, neoadjuvant therapies are increasingly becoming the standard treatment option due to their advantages. These advantages include increasing the rate of breast-conserving surgery, reducing the morbidity of surgery, providing in vivo information about the response, and giving an idea about the prognosis. Pathological complete response (pCR) is defined as no residual invasive disease on pathological evaluation of the surgical breast specimen. It has been shown that patients with a pCR have better clinical outcomes than those who do not [3]. Obtaining a pCR is related to many factors such as hormone receptor status, human epidermal growth factor receptor 2 (HER2) positivity and the chemotherapy regimen used [4].

In our country as in the rest of the world breast cancer is the most common cancer in women, and its incidence is increasing with the aging population and western-like lifestyle changes. Despite all the developments of screening and diagnostic techniques, unfortunately, due to the individual and social characteristics of our country, most of the breast cancers are diagnosed at locally advanced stages [5]. The management of breast cancer at this stage also differs due to the approach of the center to which the patient applied and the approach of the following physician.

Since most of the randomized controlled studies on NACT in the literature included young and well-performing patients, this suggests that there may be unrepresented patient groups from real life. In our study, in which we retrospectively analyzed

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Corresponding Author: Atike Pınar Erdoğan **E-mail:** dr_pinarcan@yahoo.com

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patients from medical oncology clinics of two different tertiary care centers in the Aegean region, we aimed to evaluate the effect of patient characteristics on clinical responses after neoadjuvant therapy.

METHODS

106 patients who were treated in the medical oncology clinic of two different university hospitals between 2012 - 2018 were included in our study. All patients had a biopsy-confirmed diagnosis of breast cancer and all had received NACT. Clinical and demographic data were obtained retrospectively from patient files.

Tumor histology was defined according to the World Health Organization criteria, and grading was performed according to the recent TNM Classification of Malignant Tumours (TNM) classification [6]. The expression of estrogen receptor (ER),progesterone receptor (PR), HER2 and Ki-67 was assessed using formalin-fixed paraffin-embedded tumor tissue according to international standards. pCR was defined as no residual invasive tumor on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled lymph nodes.

For the evaluation of the data obtained in the study SPSS v21.0 (Statistical Package for the Social Sciences) statistics program was used. Differences between the two groups were analyzed with the Pearson chi-square or Fisher's exact test. Categorical variables were divided into 2 groups. Predictive factors associated with pCR were analyzed by logistic regression testing. $p<0.05$ was considered statistically significant.

Ethics committee approval was obtained from the health sciences ethics committee with the decision dated 20.01.2021 and numbered 20.478.486.

RESULTS

The clinical and pathological characteristics of the 106 patients included in the study are shown in Table 1.

Majority of patients (85.8 %) had stage 3 disease. The number of patients aged 40 and under was 25 (23%), and 81 (76%) patients were over 40 years of age. The pCR was found to be 20% (5/25) in the younger group and 27.2% (22/81) in the group over 40 years of age , and this difference was statistically significant (p=0.06).

Main Points:

- Pathological response to NACT is an important factor in determining prognosis.
- The pattern of response to NACT is used to tailor systemic and locoregional treatment, therefore it is important to adapt current data to real life.
- Predicting response to NACT is essential for clinical decision making.

Table 1. Clinical and pathological characteristics of the patients

No of patients	106
Median age (range)	49 (26–75)
Histologic Type [No. (%)]	
IDC	101 (95.3)
ILC	3
Other	2
Stage [No. (%)]	
2	4 (3.8)
3	91 (89.6)
4	11 (10.4)
Preoperative T stage [No. (%)]	
1	19 (17.9)
2	64 (60.4)
3	23 (21.7)
Type Of Surgery [No. (%)]	
MRM	87 (82.1)
BCS+SLNB	7 (6.6)
MRM+SLNB	4 (3,8)
BCS+AD	8 (7.5)
Pathologic Response [No. (%)]	
Residual disease	79 (74.5)
Complete response	27 (25.5)
Chemotherapy Regimen	
Antracycline based	90 (85.8)
Other	15 (14.2)

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, MRM: Modified radical mastectomy, BSC: Breast-conserving surgery, SLNB: Sentinel lymph node biopsy

Immunohistochemical profiles of tumor tissues are shown in table 2. Hormone receptor-negative patients comprised 34% of the entire study population. It was observed that the pCR rate was higher in patients with negative hormone receptors and this difference was statistically significant (p=0.000)

The median radiological tumor diameter was 4.01±2.2 and the median pathological tumor diameter was 2.09±3.91. The median number of lymph nodes removed after NACT was 19.5±10.5 and the median number of lymph nodes with metastasis was 3.9±6.2. Median NACT duration was 5.1±1.01 months. The rate of patients with complete primary tumor response after NACT was 27.4% and the rate of patients with residual disease was 72.6%. There were 45 (42.5%) patients with axillary complete response and 61 (57.5%) patients with axillary residual disease. The rate of patients with pCR was 25.5%. No statistically significant correlation was observed between the stage of diagnosis and obtaining a pCR (p=0.062)

According to the NACT regimen used, it was observed that 85.8% received a combination of anthracycline and taxane. 28.3% (30) of the patients were HER2 positive. Trastuzumab was administered

to all HER2 positive patients in the neoadjuvant treatment protocol. pCR was 50% (15/30) in HER2 positive group.

It was observed that 28 (26%) patients developed recurrence during the follow-up, and 23 (21.7%) of them had systemic and 5 (4.7%) local recurrences. The recurrence rate of patients with pCR was 11.1%, while the recurrence rate of patients who could not obtain pCR was 31.6% (p=0.04).

The mean NACT duration applied to the patients with pCR was 5.48 ± 0.22 months, and the mean NACT duration for those who could not obtain pCR was 5.01 ± 0.1 months (p=0.041).

No correlation was observed between T stage, Ki 67 ratio, chemotherapy regimen and the pCR rate (p>0.05).

Table 2. Immunohistochemical profiles of tumor tissues

	Negative [No. (%)]	Positive [No. (%)]
ER	36 (34.0)	70 (66.0)
PR	64 (60.4)	42 (39.6)
HER2	76 (71.7)	30 (28.3)

ER: Estrogen receptors PR: Progesterone receptors
HER2: Human epidermal growth factor receptor 2

Table 3. Association between clinicopathological features and pCR

	pCR	Residual disease	P value
Stage			
2	3 (2.8)	1 (0.9)	
3	22 (20.8)	69 (65.1)	0.062
4	2 (1.9)	9 (8.5)	
Chemotherapy Regimen [No. (%)]			
Antracycline based	67 (70.5)	23 (15.2)	0.820
Other	4 (3.8)	11 (10.5)	
Hormon receptor status [No. (%)]			
Negative	19 (52.8)	17 (47.2)	**0.000**
Positive	8 (0.3)	62 (20.6)	
Ki67 Percentage [No. (%)]			
≤20	1 (1.6)	19 (29.7)	
21–50	7 (10.9)	17 (26.6)	0,057
>51	7 (10.9)	13 (20.3)	

pCR: Pathological complete response

DISCUSSION

The incidence of locally advanced breast cancer, which is 5-10% in developed countries, rises to over 50% in developing countries [7]. In a Turkish epidemiological study involving approximately 2500 patients, stage III breast cancer rate was determined as 20% [8]. In this patient group, a significant survival advantage was achieved with multidisciplinary treatment approaches, especially with the addition of NACT to the treatment [9].

Although it has been shown that breast-conserving surgery rates increase with NACT, only 7% of patients in our study group had breast-conserving surgery [10]. The advantages demonstrated by large randomized controlled trials do not appear to be reflected in the real-life population. It is seen that there is a large group of patients who did not undergo breast conserving surgery despite receiving NACT due to reasons such as high local recurrence rates, the surgeon's guidance and patient preference.

The pathological response is an important prognostic factor in determining the prognosis. Rastogi et al. demonstrated that individuals who achieved a pCR continue to have superior disease free survival (DFS) and overall survival (OS) outcomes compared with patients who did not achieve a pCR (DFS HR: 0.47, P<0.0001; OS HR: 0.32, P<0.0001)[11]. The recurrence rate of our patients with pCR was 11.1%, while the recurrence rate of patients who could not obtain pCR was 31.6% and this difference was statistically significant (p=0.04).

The addition of taxanes to anthracycline based chemotherapy regimen has shown to be superior in terms of clinical response, pathologic response, DFS and OS to the anthracycline-based regimen alone [12]. In our study, all patients received taxane, and most of them received it in combination with anthracycline. There was no statistically significant difference between anthracycline-containing regimens and taxane-only regimens in terms of pCR rates. On the other hand addition of pertuzumab to docetaxel and trastuzumab in the phase III CLEOPATRA trial resulted in a significant improvement in OS in first-line, metastatic, HER2 positive breast cancer [13]. However, since the study design was retrospective, pertuzumab was not licensed in our country in those years, so pCR rates in HER2 positive disease remained lower than in the literature.

In most Western countries, the mortality rate of breast cancer has decreased in recent years, especially in younger age groups, because of improved treatment and earlier detection [14]. In the univariate analysis performed by Öztürk et al., young age (≤40), tumor size, axilla positivity, chemotherapy regimen, pathological stage, and local recurrence were found to be important factors affecting survival [15]. In our study, pCR was found to be 20% (5/25) in the group aged 40 years and younger, and 27.2% (22/81) in the group over 40 years of age, and this difference was statistically significant (p=0.06). In the study of Spring et al., it was suggested that the achievement of pCR with NACT may be a robust marker for survival in young women with breast cancer, and the high mortality rate of 22.9% in their study population belonged mostly to patients who did not achieve pCR. They highlighted the need for better treatments for young women with breast cancer [16].

In our study, NACT duration and hormone receptor negativity were determined as factors affecting pCR. When the relationship between NACT duration and pCR was examined, it was observed that the rate of obtaining complete response increased as the

NACT duration increased, and this increase was statistically significant. The mean NACT duration applied to the patients with pCR was 5.48 ± 0.22 months, and the mean NACT duration for those who could not obtain pCR was 5.01 ± 0.1 months (p=0.041). Although the association between NACT time and pCR was demonstrated, it was not recorded whether the treatment protocols were given with a dose-intensive scheme, which is the shortcoming of the study.

Tumors that are hormone negative tend to have a higher pathologic response rate to chemotherapy than hormone positive tumors [17]. In our study group pCR was obtained in 19 of 36 hormone negative patients. On the other hand, pCR was observed in only 8 of 70 hormone positive patients. This difference was statistically significant and consistent with the literature.

Park et al. suggested in their study that negative ER status is associated with local recurrence and distant metastasis [18]. Although it is known that hormone positive tumors have less NACT response than negative tumors, in the light of the findings of Park et al. the idea of preferring more intense schemes in receptor negative patients comes to the fore in determining the treatment regimen when planning NACT.

There are some limitations of our study. First, we cannot exclude a possible selection bias as only two of the breast cancer units in the Aegean region participated. Second, we cannot say that all breast cancer patients are represented, as there is no national clinical cancer registry to which our study sample can be compared.

As a result pathological response to NACT appears to be due to the complex and unclear interplay of systemic therapy and tumor biology. Future analyses of randomized trials with targeted therapies will provide better guidance on the implementation of individualized treatments.

CONCLUSION

In conclusion, NACT should be a standard treatment in locally advanced breast cancer. Pathological response to chemotherapy is an important factor in determining prognosis. There appears to be a need for new biomarkers that allow the prediction of pCR and long-term outcomes.

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