Ankara Eğt. Arş. Hast. Derg., 2023 ; 56(1) : 11-14
DOI: 10.20492/aeahtd.1233962

Factors affecting complete response to neoadjuvant chemotherapy in triple negative breast cancer patients

Triple negatif meme kanseri hastalarında neoadjuvan kemoterapiye tam yanıtı etkileyen faktörler

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ABSTRACT

AIM: The triple negative breast cancer is a very aggressive type of breast cancer which constituting approximately 10-15% of all cases. Despite the administration of adjuvant chemotherapy, 5-year disease-free survival rates are lower than other types. Response to treatment may indicate patients' long-term outcome. Several studies are associated with pathological complete response. Improved disease-free survival and overall survival. Residual disease after neoadjuvant chemotherapy shows the tumor resistance to treatment. The aim of this study is to explore the relationship between pathological complete response and tumor characteristics.

MATERİAL AND METHOD: Data of 53 triple negative breast cancer patients who were operated at one center after neoadjuvant chemotherapy between 2015-2022 were retrospectively analyzed. The data analyzed with descriptive and inferential statistics using SPSS IBM version 25.

RESULTS: In the evaluation of 53 patients between the ages of 28 and 81 (mean: 50.7), pathological complete response was obtained in 21 of the patients (39.6 %), while 32 (60.4 %) were found to have an incomplete response or no response. Absence of axillary lymph node metastasis before neoadjuvant chemotherapy, high Ki-67 proliferation index and absence of extracapsular invasion in metastatic LN were associated with pathological complete response. Other clinicopathologic parameters were found to have no effect on the results.

DİSCUSSİON: Patients with a high Ki-67 proliferation index and no axillary involvement are more likely to have a pathological complete response after neoadjuvant chemotherapy.

CONCLUSION: It can be predicted that the prognosis may be better in patients with high Ki-67 proliferation index and no axillary involvement.

Keywords: Triple negative breast cancer, complete pathological response, neoadjuvant chemotherapy

ÖZET

AMAÇ: Triple negatif tip meme kanseri, tüm meme kanseri vakalarının yaklaşık % 10-15' ini oluşturan çok agresif bir meme kanseri türüdür. Adjuvan kemoterapi uygulamasına rağmen 5 yıllık hastalıksız sağ kalım oranları diğer tiplere göre daha düşüktür. Tedaviye yanıt hastaların uzun vadeli sonuçlarını gösterebilir. Bazı çalışmalara göre patolojik tam yanıt hastalıksız sağkalım ve genel sağkalım ile ilişkilidir. Neoadjuvan kemoterapi sonrası rezidüel hastalık tümörün tedaviye direncini gösterir. Bu çalışmanın amacı, patolojik tam yanıt ile tümör özellikleri arasındaki ilişkiyi araştırmaktır.

GEREÇ VE YÖNTEM: 2015-2022 yılları arasında tek merkezde neoadjuvan kemoterapi sonrası opere edilen 53 tripl negatif meme kanseri hastasının verileri retrospektif olarak incelendi. Veriler, SPSS IBM sürüm 25 kullanılarak tanımlayıcı ve çıkarımsal istatistiklerle analiz edildi.

BULGULAR: Yaşları 28-81 arasında olan (ortalama: 50,7) 53 hastanın değerlendirilmesinde, hastaların 21' inde (%39,6) patolojik tam yanıt elde edilirken, 32' sinde (%60,4) kısmi yanıt alındığı veya yanıt alınamadığı saptandı. Neoadjuvan kemoterapi öncesi aksiller lenf nodu metastazı olmaması, yüksek Ki-67 proliferasyon indeksi ve metastatik LN'de ekstrakapsüler invazyonun olmaması patolojik tam yanıt ile ilişkili olarak tespit edildirken diğer klinikopatolojik parametrelerin sonuçlara etkisi olmadığı görüldü.

TARTIŞMA: Ki-67 proliferasyon indeksi yüksek olan ve aksiller tutulumu olmayan hastaların neoadjuvan kemoterapiden sonra patolojik tam yanıt alma olasılığı daha yüksektir.

SONUÇ: Eldeki veriler incelendiğinde Ki-67 proliferasyon indeksi yüksek olan ve koltuk altı lenf nodu tutulumu olmayan hastalarda patolojik tam yanıtın yüksek olması nedeniyle prognozun da daha iyi olabileceği öngörülebilir.

Anahtar Kelimeler: Triple negatif meme kanseri, patolojik tam yanıt, neoadjuvan kemoterapi

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Makale Geliş Tarihi / Submitted: Ocak 2023 / January 2023

Makale Kabul Tarihi / Accepted: Şubat 2023 / February 2023

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Note: The results of the study were presented as an oral presentation at the 22nd National Surgery Congress held in Antalya between 23-27 March 2022.

INTRODUCTION

Breast cancer is the most common solid tumor affecting women, and it's the second leading cause of cancer - related mortality for this group 1. Triple-negative breast cancer (TNBC) is defined histologically as invasive cancer of the breast that lacks staining for estrogen and progesterone receptors (ER and PR), and human epidermal growth factor receptor - 2 (HER2/neu). There about 15-20 % of breast carcinomas illustrate this phenotype [2]. Neoadjuvant chemotherapy (NAC) is being used for patients with TNBC with the purpose of achieving pathological complete response (pCR), because patients who have a pCR have improved disease free survival (DFS) compared with the patients that have residual disease in the breast or lymph nodes [3]. Several studies are associated with pCR improved DFS and overall survival (OS) [4]. Tumor characteristics that affect the response to NAC are the absence or low expression of hormone receptors, high Ki-67 or high grade and ductal pathology[5]. pCR rate varies in primary tumor and axillary lymph node according to tumor subtypes. Tumor subtypes are determined by the hormone receptors (ER and PR) and human epidermal growth factor receptor - 2 (HER2) statues. HER2 overexpressed or hormone receptor negative or triple negative tumors respond better to NAC [6]. It has been found that the presence of elevated Ki-67 prior to NAC predicts the response to chemotherapy in locally advanced breast cancer. Studies have shown that patients with high Ki-67 levels are an independent factor in predicting pCR after NAC [7]. NAC increases the patient's survival by causing a pCR in breast cancer. Residual disease after NAC shows the tumor resistance to treatment. Although the pCR is high in TNBC, they are heterogeneous cancers, their response to treatment may be different 8. Anticipating TNBC that will give an incomplete response to the treatment before chemotherapy may lead to the application of different protocols such as adding other treatments to the NAC protocol, increasing the dose or extending the duration of chemotherapy.

MATERIAL AND METHOD

This is a descriptive study conducted at one center, and it's approved by the local non–invasive studies ethics committee. All the patients released a written informed consent. In our study, we retrospectively collected clinical, pathological, radiological information of TNBC patients who underwent NAC at the general surgery department of university hospital. Between January 2015 and May 2022, 804 patients were operated for breast cancer in our center, 80 of patients (%10) which were triple negative and 53 of 80 patients (% 66.3) received NAC. This number and ratios are seen that our TNBC rate is compatible with the literature 9. A retrospective review of radiologic, clinic and pathologic data were collected to a database. These data were including demographic, clinical and molecular specifications, tumor diameter before NAC, axillary node involvement status at baseline, defined by physical examination and ultrasound with a needle biopsy if necessary. The initial stage was determined via these data evaluation; and classification made according to the National Comprehensive Cancer Network (NCCN) TNM guidelines. All the patients had a diagnosis of TNBC by a tru-cut biopsy. Complete pathology assessment including receptors, HER2/neu status and Ki-67 indexes, were done in pre-treatment biopsy. pCR defines the absence of any residual tumor cells in breast by a histologic evaluation of a tumor specimen . pCR at definitive surgery was defined as the lack of invasive breast cancer in the breast; pathological responses were evaluated according to the Miller - Payne classification system 10. There are 5 subgroups in the Miller-Payne staging system and grade 1 means no response to NAC, while grade 5 means that the tumor has a pCR to neoadjuvant treatment. Axillary lymph nodes positiviy was revealed by fine needle aspiration biopsy. The presence of residual in situ carsinoma was also included in the pCR definition. Grade was based on the modified Nottingham histological scoring system and divided into three grades (1, 2 and 3 for well, moderate, or poorly differentiated respectively). The relationship between age, tumor size before NAC, vitamin D level (N : >30 ng/ ml), axillary lymph node involvement, histologic type and Ki-67 level on response were evaluated.

The inclusion criteria of our study were female patients, 18 years of age or older who received NAC for stage I-IV TNBC. The collected data analyzed using descriptive statistics and categorical data were compared by t-test, chi square and fisher exact test, using IBM SPSS Statistics version 25.0 software to identify any significant prognostic factors for pCR in TNBC patients. P value < 0.05 was considered significant.

RESULTS

The information's of 53 TNBC patients since 2015 to 2022 were included in this study. Patient characteristics, the comparison of clinical, radiological and pathological characteristics between the pCR (+) and pCR (-) groups were shown in the Table I.

Table 1: Patient characteristics; association of baseline clinical characteristics with pathological response in tumor.

	N (%)	pCR (-), %	pCR (+), %	p- value
Age				
<50	26 (49.1)	18 (56.25)	8 (38.09)	0.470
≥50	27 (50.3)	14 (43.75)	13(61.90)	
Tumor size				
≤2 cm	7 (13.2)	4 (12.5)	3 (14.2)	0.477
2-5cm	37 (69.8)	21 (65.62)	16 (76.1)	
>5 cm	9 (17.0)	7 (21.87)	2 (9.5)	
Histological type				
Invasive ductal	45 (84.9)	27 (84.3)	18 (85.7)	0.810
Other	8 (15.09)	5 (15.7)	3 (14.3)	
Grade				
1	7 (13.2)	5 (15.6)	2 (9.5)	
2	14 (26.4)	9 (28.1)	5 (23.8)	0.268
3	32 (60.3)	18 (56.25)	14 (66.6)	
Ki-67				
<15	3 (5.6)	2 (7.6)	1 (5.9)	
15-29	6 (11.2)	5 (19.2)	1 (5.9)	0.357
≥30	34 (64.1)	19 (73.1)	15 (88.2)	
Unknown	10 (18.8)			
Axillary lymph nodes				
Negative	34 (64.1)	14 (43.75)	20 (95.2)	**0.002**
Positive	19 (35.9)	18 (56.25)	1 (4.8)	
Extracapsular Invasion				
Negative	11 (68.8)	1 (16.7)	10 (100)	0.214
Positive	5 (31.2)	5 (83.3)	0 (0)	
Vitamin D level (N:> 30ng/ml)				
Low	36 (67.9)	21 (91.3)	15 (83.3)	0.331
Normal	5 (9.4)	2 (8.7)	3 (16.6)	
Unknown	12 (22.6)			

The mean age of patients was 50.7 (28-81). Number of patients who showed pCR in the breast was 21 (39.6 %). In the group with Ki-67 level above 30%, 44.1% pCR was obtained, while in the group below 30% pCR was 22.2%. We did not determine a significant difference (p:0.357). Pathological axillary lymph node involvement seen in 19 patients and in this group pCR rate was 5.2 %; in the group including 34 patients without axillary involvement, the pCR rate was 58.8%, it's found that is a predictive factor for pCR (-) (p<0.01). Although the pCR rate was found with the highest rate with a rate of 43.2% in tumors between 2-5 cm, there was no statistically significant difference when compared with tumors larger than 5 cm or smaller than 2 cm (p=0.477). While the rate of pCR was 33.3% in the group with low vitamin D levels (36 patients), the rate of pCR was found to be 60 % in the group with high or normal vitamin D levels (5 patients), but statistically there was not any difference between two groups. (p=0.331). pCR was higher in women with high grade tumors than low grades but statistically no difference found (p=0.268) between the groups. The extracapsular involvement of the metastatic LN didn't cause any difference at pCR (p=0.261). Because of 93% of the tumors were invasive ductal carcinoma, a comparison group could not be created, and further comments were not made on this subject. The highest pCR was obtained in patients without pathological axillary involvement and with a high Ki-67 proliferation index. On the other hand, Vitamin D level, patient's age, the tumor size before NAC and other clinicopathological factors were found not to have no effect on the pCR.

DISCUSSION

Although TNBC has an overall bad prognosis, these patients having NAC have

improved organ conservation rates [11]. Neoadjuvant chemotherapy (NAC) has been widely utilized in treatment of breast carcinoma, and pathological diagnosis after surgery contributed to evaluation of curative effect. Some clinicopathological characteristics and treatment related factors may take essential role in tumor response to NAC [12]. This study describes a retrospective analysis of factors affecting pCR outcomes in patients who treated with NAC for TNBC. In the study, having a higher Ki-67 proliferation index and the absence of axillary involvement were found to be the most effective findings on pCR to NAC. It has been widely recognized that axillary lymph nodes involved after NAC plays a very important role in the prognosis of TNBC patients. Axillary lymph nodes response to NAC is an important component of pathological evaluation [12]. In our study, the patients that had extracapsular invasion in axillary LN had no pCR in tumor. If capsular invasion can be detected at initially by ultrasound, it can be predicted that which patients will have complete response or not. Although there was no statistically significant result, it was thought that this was related to the low number of patients. This finding may change the way to be followed in treatment in terms of protecting the axilla. Xiaoxian et al. reported a notable relation between pCR and ki-67 proliferation index level both as a categorical variable especially when <15 % was set as the cut-off value for defining higher Ki-67 proliferation index. Their findings were similar to other studies and ours 7. Several studies were conducted on the proliferation index of Ki-67 but there are relatively few trials addressing the question of the role of Ki-67 in patients who did not achieve pCR. There appear to be some inconsistent data concerning Ki-67 as a prognostic factor in breast cancer patients underwent NAC [13]. Denkert et al. suggests Ki-67 may be considered a both predictive and prognostic marker, although it's effect is the opposite when it comes to prediction or prognosis [14]. Another retrospective study was carried out in 120 TNBC patients who treated with NAC. Trial results have confirmed that higher Ki-67 levels are associated with increased response to NAC and also with worse long - term outcome in patients who pCR (-)[15]. Breast carcinoma is characterized based on expression of the estrogen (ER), progesterone (PR) and human epidermal growth factor - 2 (Her-2) receptors. There are 4 subtypes which patients with breast cancer can be divided into based on their tumor markers: Luminal A, luminal B, Her-2 or triple negative (TN) type 16. Molecular typing of tumors has allowed clinicians to make clinical decision and make risk stratification. In a meta-analysis including 14.000 patients done by Haque et al. it's found that the pCR rate was 19 %; lowest in luminal- A disease (0.3%), the highest in Her-2 type disease (38.7 %) and second highest in TNBC (23.2%). Molecular profiling is a powerful independent prediction factor of pCR and overall survival (OS) 17. We see more than 38.1% complete pCR in our surgical series. Axillary complete response rate was determined as 58.8 %. This ratio proves that if surgery is performed without NAC, unnecessary axillary lymph node dissection and large mastectomies can be performed. Therefore, NAC should come first in TNBC patients in case of tumor diameter larger than 1 cm and/or axillary involvement. In our study 37% of patients were under age of 50 at the time diagnosis and 63% older than 50 years. There wasn't any difference between two groups in terms of pCR which support our findings too. Olfatbakhsh et al were found no significant difference between pre or postmenopausal status in terms of pCR [18]. Biswas et al. detected a differential response rate of TNBC to NAC based on tumor stage, with less pCR observed among women with advanced cancer stage. For patients with stage II disease, the pCR rate was 53 % and 19 % for stage III disease. Their study shows a decreasing pCR rate following NAC with advancing tumor stage 19. Gass et al. reported that pCR rate was higher in women with clinically smaller tumor diameters, histological grade 3, and high Ki-67 proliferation levels 20. However, in our study, a statistically significant relationship could not be established between tumor grade or tumor size with pCR. This may be because we rely on a relatively small number of patient groups. Some studies reported a protective role for vitamin D in breast carcinoma development 21. Vitamin D has been shown to induce cell-cycle arrest via increasing the expression of cyclin- dependent kinase (CDK) inhibitors (p21 or p27) in breast cancer cell lines. Active vitamin D metabolites also can regulate the expression of oncogenes c-fos and c-myc 22. Low vitamin D levels were detected in 67.9 % of the patients, and this rate was considered to be higher than the general population. Rainville et al concluded that the TNBC subtype has the lowest average vitamin D levels. This data suggests that low levels of vitamin - D is characteristic of the TNBC 23. In our study, we demonstrated that the level of vitamin - D was found to be lowest in TNBC patients compared to other luminal types. Most of patients had low level of vitamin D but there was no statistically difference in term of pCR. In our study, negative axillary lymph nodes before NAC was found to be a positive predictive marker suggesting a pCR, as Kern et al. similarly stated before [24]. We also determinded that the high Kİ-67 level have positive affect in the pCR but no significant difference found. The presence of extracapsular invasion seems to reduce the likelihood of a pCR. But it should be noted that this study has some limitations; because it's a retrospective study which includes low number of patients.

CONCLUSION

Patients who have a higher Ki-67 proliferation index and lack of axillary involvement are more likely to have a pCR after NAC. We have confirmed the potential use of Ki-67 as a predicting factor for response to NAC. Ki67 >30% was slightly associated with better response to NAC and relatively worse prognosis. Therefore, it can be important to measure the Ki-67 index, which can be used as a marker in the treatment and follow-up of breast cancer. pCR can be considered a reasonable factor for prediction of tumor response and prognosis of the patients.

Author contribution:

AK, BK: Conceived and designed the experiment, performed the experiments, wrote the paper.

YA: Contributed reagents, materials, analysis tools or data, statistical calculation.

BK: Review & editing, supervision, project administration.

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