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Research Article

Response Rates and Predictive Factors of Pathological Complete Response to Neoadjuvant Chemotherapy in Luminal B HER2 Negative Breast Cancer

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Abstract

Objectives: In breast cancer, pathological complete response (pCR) to neoadjuvant chemotherapy showed association with overall survival. However, this relationship varied according to the tumor's receptor status and pathological features. In this paper we aimed to show response rates and predictive factors of pCR in luminal B HER2 negative breast cancer patients who received neoadjuvant chemotherapy (NC).

Methods: We have searched the database retrospectively January 2015 and January 2020. Inclusion criteria for this study were women newly diagnosed, nonmetastatic ER positive, HER2 negative, PR positive or negative, ki67 ≥%20, T1-4 N1-3 breast cancer treated with NC followed by surgery and RT. All patients received regimen containing antracycline.

Results: 82 patients met study criteria in our center. Invasive ductal carcinoma was the predominant tumor type (%77.5). pCR was achieved in only 12 patients (%14.6). In univariate analysis, factors associated with pCR were absence of LVI (p=0.003) and high grade of the tumor (p=0.002). Median OS and median EFS could not be reached. There was no death from patients with pCR.

Conclusion: This study suggest that the presence of LVI is associated with poorer response, presence of high grade is associated with good response to NC in HER2 negative Luminal B breast cancer patients.

Keywords: Breast cancer, Neoadjuvant chemotherapy, Luminal B, HER2 negative

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Breast cancer became the most common cancer globally as of 2021, accounting for 12% of all new annual cancer cases worldwide, according to the World Health Organization.[1] Breast cancer has subtypes molecularly characterized based on expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2). These subtypes are Luminal A, Luminal B (HER2 -), Luminal B (HER2 +) and triple negative. Hormone-positive tumors are classified as luminal A or luminal B subtypes and distinguished by the Ki-67 proliferation index, which is higher in the luminal B subtype.[2] A threshold of Ki-67 of 14 percent was earlier established for the distinguishing of luminal A and luminal B intrinsic subtypes, but a majority of the panel decided that a threshold of 20 percent is suggestive of high Ki-67 status based on a comparison using gene array data.[3]

Neoadjuvant systemic therapy is indicated in women with inflamatuary breast cancer, T4 tumors, N2, N3 nodal disease. But there were no significant differences in long-term outcomes whether systemic chemoterapy was given before or after surgery, according to randomized clinical trials.[4,5] So when patient desires breast conserving surgery but the surgery is impossible due to the size of the tumor relative to her breast, neoadjuvant therapy could be preferred. The goal of this study was to indicate the response rates and predictive factors for neoadjuvant chemotherapy in Luminal B HER 2(-) breast cancer patients.

Methods

Patients and Chemotherapy

We have searched the database of the Department of Medical Oncology in Istanbul Research and Training Hospital between January 2015 and January 2020. We have obtained the approval of the local ethics committee to conduct a human investigation, and conducted this study retrospectively in accordance with the ethical principles set forth by the Declaration of Helsinki. Women newly diagnosed, nonmetastatic ER positive, HER2 negative, PR positive or negative, ki67 ≥ %20, T1-4 N1-3 breast cancer treated with neoadjuvant chemoterapy followed by surgery and RT were included in the study. All patients received regimen containing antracycline (FEC100 5FU 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2/q3w, 4 courses) and taxanes (paclitaxel 80 mg/m^2/qw, 12 courses or docetaxel 75 mg/m^2/ q3w, 4 courses) or ACT (Doxorubisin 60 mg/m^2, cyclophosphamide 500 mg/m^2/q3w, 4 courses) and taxanes (paclitaxel 80 mg/m^2/qw, 12 courses or docetaxel 75 mg/m^2/ q3w, 4 courses).

Pathologic specimens were obtained by the 14G-core needle biopsy from all patients. ER, PR positivity were determined as a ratio of positive cells to total cancer cells. A value of 10% or higher were rated as positive. HER-2 expression is defined as negative if it is (0) or (1+) based on positive cell rates and the intensity of IHC staining. HER2 (2+) were also tested by Fluorescence in situ hybridization (FISH) method to determine the gene amplification of the HER-2. Ki-67 score is defined as the percentage of positively stained cells among the total number of malignant cells scored.[6]

After neaoadjuvant chemotherapy, all patients underwent surgical treatment. Pathologic complete response (pCR) was defined as no residual invasive tumor cells found in breast tissue or axillary lymph nodes (ypT0/ ypN0). Patient with no response or partial response were defined as no-pCR. Overall survival (OS) was defined as the time elapsed from the time of the first pathological diagnosis until the time of the death. Event free survival (EFS) was defined as the time elapsed from the time of the first pathological diagnosis until the time of the first event of recurrent disease.

Statistical Analysis

Commercial software (SPSS version 20.0®, SPSS, Chicago IL, USA) was used for the statistical analysis. Standard descriptive statistics were used to summarize all variables. The Kolmogorov–Smirnov test was used to analyse the normal distribution of data. For the univariate analyses, Chi-square test was used. Kaplan-Meier plots were used to analyse survival data. P values <0.05 were accepted as statistically significant.

Results

From 2015 to 2020, 82 patients met study criteria in our center. The median age of patients was 50.5 (min 30-max 76). %51.2 patients were postmenapousal. Clinical and pathological characteristics of the patients are shown in the Table 1. pCR was achieved in only 12 patients (%14.6). No clinical progression was seen in any patient. Clinical partial response was seen in 63 (%76.8) patients, clinical stable disease was seen in 7 patients (%8.5). Invasive ductal carcinoma was the predominant tumor type (%77.5). Regarding the tumor stage, the majority of patients had T1/ T2 tumors (%78.1), %21.9 were T3/T4. 9 (%11) patients had N3, 47 (%57.3) patients had N2 and 26 (%31.7) patients had N1 tumor. All patients have ER (+) tumor, only 12 patients (%14,6) have PR (-) tumor. LVI (lymphovascular invasion) was reported in 36.6 percent of cases. PNI (perineural invasion) was reported only in 4.9 percent of cases. %72 of patients received FEC protocol and %28 patients recieved ACT protocol. %57.4 patients had grade 2 tumor, %42.7 patients had grade 3 tumor.

In univariate analysis, factors associated with pCR were

Table 1. Characteristics of Patients

	All patients, No (%)	pCR, No (%)	No pCR, No (%)	p
	82 (100)	12 (14.6)	70 (85.4)	
Age, median	50.5	47.5	51.5	
T1,T2	64 (78.1)	9 (75)	55 (78.6)	0.720
T3,T4	18 (21.9)	3 (25)	15 (21.4)	
N1	26 (31.7)	2 (16.7)	24 (34.3)	0.322
N2,N3	56 (68.3)	10 (83.7)	46 (65.7)	
ER				a
positive	82 (100)	12 (100)	70 (100)	
negative	0 (0)	0 (0)	0 (0)	
PR				
positive	70 (85.4)	11 (91.7)	59 (84.3)	0.684
negative	12 (14.6)	1 (8.3)	11 (15.7)	
Menopausal status				
PRE	40 (48.8)	6 (50)	34 (48.6)	0.927
POST	42 (51.2)	6 (50)	36 (51.4)	
LVI				
positive	30 (36.6)	0 (0)	30 (42.9)	0.003
negative	52 (63.4)	12 (100)	40 (57.1)	
PNI				
positive	4 (5.7)	0 (0)	4 (5.7)	1.0
negative	66 (94.3)	12 (100)	66 (94.3)	
Family History				
Yes	8 (9.8)	3 (25)	5 (7.1)	0.089
No	74 (90.2)	9 (75)	65 (92.9)	
Grade				
2	47 (57.4)	2 (16.7)	45 (64.3)	0.002
3	35 (42.7)	10 (83.3)	25 (35.7)	
Protocol				
FEC	59 (72)	9 (75)	50 (71.4)	1.0
ACT	23 (28)	3 (25)	20 (28.6)	

a. No statistics are computed.

absence of LVI (p=0.003) and high grade of the tumor (p=0.002).

Median OS and median EFS could not be reached (Figs. 1, 2). There was no death from patients with pCR. Only 3 patients died in no pCR group. There was no signficant differences between pCR and no pCR in terms of OS and EFS, p=0.463, p=0.708, respectively).

Discussion

This study showed that lymphovascular invasion and being low grade are significantly associated with unfavorable response to neoadjuvant chemotherapy in HER-2 negative luminal B breast cancer patients. %14.6 patients have experinced pCR in this study. Khalid Al-Saleh et al. found 35.5% pCR after neo CT (neoadjuvant chemotherapy) in luminal B breast cancer. Their study contains only 31 patients.[7] Mauricio Rivas et al showed %23 pCR after neo CT in luminal B breast cancer. Their number of patients with luminal B was 34.[8] Pegah Sasanpour et al. included all patients receiving neoadjuvant chemotherapy in the study and achieved a pathological complete response of 39.2%. %35.5 of patients had HER + disease in this article.[9] Rastogi et al.[10] in their studies found that pCR was found in %13 of patients when received AC, %26 of patients when received AC-T. Waqar Haque at al.[11] in their study of 13,939 patients, 8.3% of patients with luminal B and her2 negative showed pCR. The overall pCR rate was 19% in that study. In the CTneoBC study.[12] hormone positive, HER2 negative high grade, luminal B population experienced pCR in 16.2%. Additionally, this study defined pCR as ypT0, whereas CTneoBC allowed for ypTis.

This study showed that factors associated with pCR were

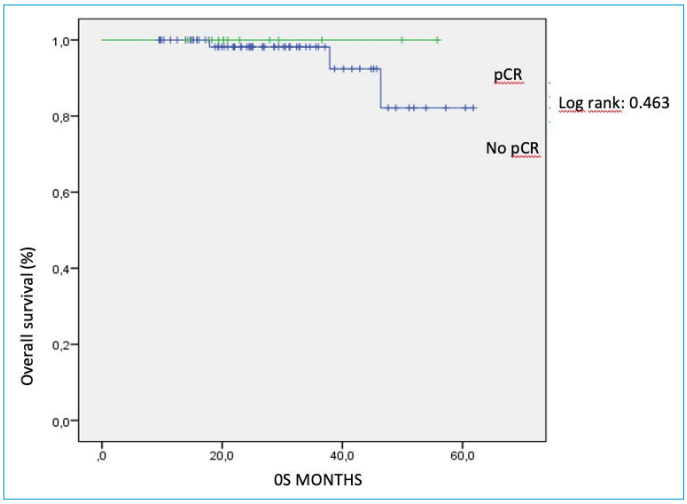

Figure 1. Median OS could not be reached. There was no signficant differences between pCR and no pCR in terms of OS, p=0.463.

OS: Overall survival; pCR: pathological complete response

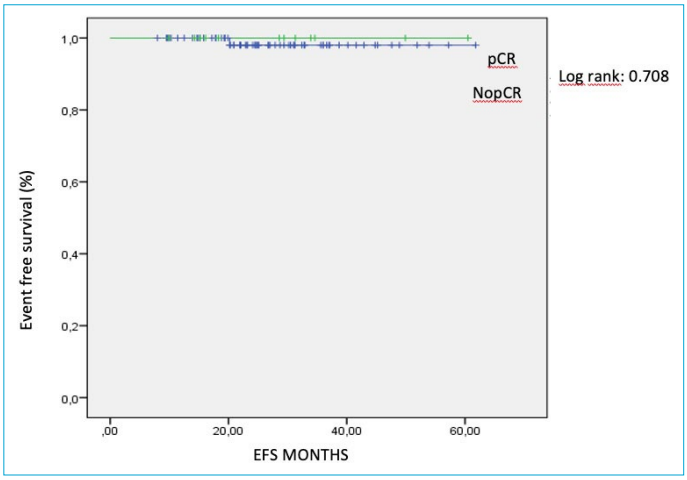

Figure 2. Median EFS could not be reached. There was no signficant differences between pCR and no pCR in terms of EFS, p=0.708.

EFS: Event free survival, pCR: pathological complete response.

absence of LVI and high grade of the tumor. The results of our study are similar to prior studies of LVI in breast cancer patients receiving neoadjuvant chemotherapy. Uematsu et al,[13] Keskin et al,[14] Abdel-Fatah[15] et al. showed that LVI is associated with chemoresistant breast cancer. Our study also showed that absence of LVI is associated with pCR.

We know that the highest increase of pCR chance was observed in patients with high-grade tumours, even this has proven by many studies.[16,17] We showed in this study that high grade tumors are associated with pCR.

In all patients we did not reach median OS and EFS. There were no signficant differences between pCR and no pCR in terms of OS and EFS. However we know that those with pCR have a longer life expectancy than those with no pCR. In CTneoBC study they found that patients who achieved pCR had longer EFS and OS than did patients with residual invasive cancer.[12]

Although previous studies have reported higher pCR with smaller clinical tumor size,[14,18] we did not find such data while T1/T2 lessions were predominant in this study.

This study had some limitations. First limitation was that it was carried out as a retrospective study based on the medical records of patients. So we couldn't assess causality and could only show correlations. The second limitation of this study was that the number of patients included was small and medical records of most patients could not be obtained.

In conclusion this study suggests that the presence of LVI is associated with poorer response, presence of high grade is associated with good response to neoadjuvant chemotherapy in HER2 negative Luminal B breast cancer patients.

Disclosures

Ethics Committee Approval: Istanbul Training and Research Hospital. A decision numbered 2894 of 30.07.2021.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – N.S.S.; Design – N.S.S., F.D.C.T., O.M., E.A.; Supervision – N.S.S., M.B.U., R.U.G., Y.B., E.C., S.B.H.; Materials – O.M., N.S.S., R.U.G., Y.B., C.K., M.B.U., S.B.H.; Data collection &/or processing – C.K., N.S.S.; Analysis and/or interpretation – N.S.S., F.D.C.T., E.A., S.B.H.; Literature search – N.S.S., E.C.; Writing – N.S.S.; Critical review – N.S.S., R.U.G., Y.B., E.A., F.D.C.T., M.B.U., S.B.H., E.C.

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