ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210114

Factors affecting pathological complete response after neoadjuvant chemotherapy in breast cancer: a single-center experience

Ozlem Mermut[1]*, Berrin Inanc[1], Rıza Umar Gursu[2], Esra Arslan[3], Didem Can Trabulus[4], Semiha Battal Havare[5], Melis Baykara Ulusan[6]

SUMMARY

OBJECTIVE: The aim of this study was to examine the characteristics of patients admitted to our hospital with a diagnosis of breast cancer who reached pathological complete response after being operated following eight cycles of neoadjuvant chemotherapy.

METHODS: Between 2015–2020, patients with pathological complete response who were operated on after neoadjuvant chemotherapy and sent to our clinic for radiotherapy were evaluated.

RESULTS: The median age of the patients was 51 years. The most common histological type was invasive ductal cancer. The number of pathological complete response patients was 74 (28%), and the number of non-pathological complete response patients was 188 (72%). Patients with pathological complete response had a smaller tumor diameter than the non-pathological complete response group (p=0.001). For pathological complete response, T1 stage, N1 stage, NG 3, Ki-67 >20%, negative estrogen receptor, negative progesterone receptor, positive Cerb-B2, and adding trastuzumab to chemotherapy were statistically significant (p<0.05). Before neoadjuvant chemotherapy, stage T1–T2 (p=0.036), LN0–1 (p=0.026), Cerb-B2 positivity (p=0.025), and an initial nuclear grade of three (p=0.001) were found to be the factors affecting pathological complete response.

CONCLUSIONS: With neoadjuvant chemotherapy, the size of locally advanced tumors decreases, allowing breast conserving surgery. The neoadjuvant chemotherapy response can be used as an early indicator of the prognosis of patients with breast cancer. Today, neoadjuvant chemotherapy is also used for patients with early-stage, operable breast cancer because it has been shown in many studies that reaching pathological complete response is associated with positive long-term results. If we can identify patients who have reached pathological complete response before neoadjuvant chemotherapy, we think we can also determine a patient-specific treatment plan at the beginning of treatment.

KEYWORDS: Breast cancer. Neoadjuvant chemotherapy. Treatment.

INTRODUCTION

Of all cancers, breast cancer has the second highest death rate in women[1]. Neoadjuvant chemotherapy (NAC) first began to be used for locally advanced, inoperable breast cancers. Then, it was used to reduce the tumor size and achieve good cosmetic outcomes. NAC treats systemic micrometastatic disease from the beginning and reduces the tumor burden within the breast and axillary lymph nodes[2]. Currently, it is also used for patients

[1]University of Health Sciences Istanbul Training and Research Hospital, Department of Radiation Oncology – Fatih, Istanbul.
[2]Acıbadem Bakırköy Hospital, Department of Medical Oncology – Bakırköy, Istanbul.
[3]University of Health Sciences Istanbul Training and Research Hospital, Department of Nuclear Medicine – Fatih, Istanbul.
[4]University of Health Sciences Istanbul Training and Research Hospital, Clinic of General Surgery – Fatih, Istanbul.
[5]University of Health Sciences Istanbul Training and Research Hospital, Clinic of Pathology – Fatih, Istanbul.
[6]University of Health Sciences Istanbul Training and Research Hospital, Department of Radiology – Fatih, Istanbul.
*Corresponding author: mermutozlem@gmail.com
Conflicts of interest: the authors declare there are no conflicts of interest. Funding: none.
Received on April 11, 2021. Accepted on April 20, 2021.

with small tumors. Since an intermediate assessment is performed during NAC, it provides early awareness of a nonresponsive tumor and provides an opportunity to terminate non-useful treatment and/or switch to an alternative treatment[3]. Tumors with high proliferation rates and negative hormone receptors are more sensitive to chemotherapy and are more likely to be within the pathological complete response (pCR) group[4,5]. It is believed that tumors with Her2-positive and triple-negative (TN) subtypes have higher (60–80%) pCR values; whereas luminal A subtype tumors are the least likely to achieve pCR[4-6]. This study aimed to evaluate patients who reached PCR at the end of the NAC and to illustrate the clinical and pathological factors affecting pCR.

METHODS

Between 2015–2020, patients with pCR who were operated on after NAC and sent to our clinic for radiotherapy were evaluated. The exclusion criteria for this study were as follows: bilateral breast cancer, male breast cancer, other malignancies, and metastatic breast cancer. This study was approved by the Ethics Committee (2614/2020) of our hospital. Disease-free survival (DFS) was assessed at the time before metastasis or local recurrence, while the overall survival (OS) was assessed at the final follow-up or the time before death.

Clinical assessment

Breast masses were diagnosed with a tru-cut biopsy. Patients who were radiologically and/or clinically positive for lymph nodes were administered a fine needle aspiration biopsy. We used Black's nuclear grade system. When there was no evidence of a residual invasive tumor in the breast or axillary lymph nodes (ypT0N0/ypTisN0) using the Miller–Payne classification, the histological response to NAC was considered to be pCR[7]. A categorization of Miller–Payne grade five was made when no malignant cells from the tumor were present and only vascular fibroelastotic stroma persisted. Nevertheless, ductal carcinoma *in situ* may be present, and estrogen receptor (ER) and progesterone receptor (PgR) statuses were assessed by immunohistochemical analysis; tumor cells ≥1% were counted as positive. Tumors were deemed Her2 (human epidermal growth factor)-positive with a Cerb-B2 score of 3+(powerful homogeneous staining). For the 2+score (medium homogeneous staining), amplification was described by the chromogenic *in situ* hybridization approach. After the fourth and the eighth chemotherapy treatments, clinical and radiological response diligence was done. Anthracycline-based agents were preferred in the first four cycles, and taxane-based agents (±trastuzumab) were preferred in the next four cycles. Initial 18-fluorodeoxyglucose positron emission tomography for staging was performed on 80% of patients. Tumors were evaluated by the staged tumor node metastases method (7th edition).

Statistical analysis

Statistical analyses were carried out with the help of the SPSS version 26.0 program. The compatibility of variables with normal distribution was studied using the Kolmogorov–Smirnov test. Mean, SD, and median values were used when presenting descriptive analyses. Categorical variables were compared with the Pearson's chi-squared test. The Mann-Whitney U test was used when evaluating nonparametric groups. The survival analysis of pCR was studied with the Kaplan–Meier estimator. The factors affecting the complete response were studied with the binary logistic regression. Cases where the p-value was below 0.05 were evaluated as statistically significant results.

RESULTS

The median age of the patients was 51 years (range: 25–76 years). The number of pCR patients was 74 (28%), and the number of non-pCR patients was 188 (72%). The most common histological types were invasive ductal cancer (IDC, n=213), invasive lobular carcinoma (ILC, n=14), apocrine carcinoma (n=13), mixed type (IDC+ILC, n=8), invasive micropapillary carcinoma (n=6), metaplastic carcinoma (n=5), and mucinous cancer (n=3). Patients with pCR had a smaller tumor diameter than non-pCR group (p=0.001). For pCR T1 stage, N1 stage, nuclear grade (NG) 3, Ki-67>20%, negative ER, negative PgR, positive Cerb-B2, adding trastuzumab to chemotherapy was statistically significant (p<0.05). But, there was no difference between the groups in terms of radiation dose and menopausal status (p>0.05). Mastectomy patients received 50 Gy of radiation (62% pCR and 57% non-pCR group); 60–66 Gy of radiation (38 pCR and 43% non-pCR group) was given to patients with breast conserving surgery (BCS). All patients received RT. Distant metastasis was observed more frequently in those who did not achieve pCR (p=0.011). The most common location of metastasis was bone (n=8), and the second most common location was the brain (n=7) and lymph nodes (n=7), followed by the liver (n=4), the lung (n=3), and local recurrence (n=3). Our pCR rate was 28%. The general characteristics of patients are shown in Table 1.

The 5-year DFS was 87% in the pCR group and 65% in the non-pCR group (p=0.023). The 5-year OS rate was 98% in the pCR group and 48% in the non-pCR group (p=0.033) (Figure 1). The factors affecting pCR were examined with the binary logistic regression. Before NAC, stage T1–T2 (p=0.036), LN0–1 (p=0.026), Cerb-B2 positivity (p=0.025), and an initial nuclear grade of three (p=0.001) were found to be the factors affecting pCR (Table 2).

Table 1. General characteristics for pathological complete response pathological complete response and non-pathological complete response groups.

	Complete response (present) n (%)	Complete response (absent) n (%)	p-value
Age	49±10.2	51±9.5	0.792
Tumor diameter	3.0±3.7	4.0±4.4	0.001
Histology			
Invasive ductal cancer	63 (85)	150 (80)	0.318
Others	11 (15)	38 (20)	
T stages			
T1	15 (20)	10 (5)	0.002
T2	45 (61)	121 (64)	
T3	6 (8)	24 (13)	
T4	8 (11)	33 (18)	
Lymph node stages			
N0	4 (5)	8 (4)	0.015
N1	30 (41)	49 (26)	
N2	36 (49)	95 (51)	
N3	4 (5)	36 (19)	
Nuclear grade			
1	0 (0)	7 (4)	<0.001
2	16 (22)	96 (51)	
3	58 (78)	85 (45)	
Ki-67 ratio			
Unknown	6 (8)	25 (13)	0.014
≤20	6 (8)	39 (21)	
>20	62 (84)	124 (66)	
Estrogen receptor			
Positive	43 (58)	149 (79)	<0.001
Negative	31 (42)	39 (21)	
Progesterone receptor			
Positive	40 (54)	129 (69)	0.027
Negative	34 (46)	59 (31)	
Cerb-B2 status			
Positive	39 (53)	44 (23)	<0.001
Negative	35 (47)	144 (77)	
Chemotherapy			
4 AC+4 docetaxel	30 (40)	137 (73)	<0.001
4 AC+12 paclitaxel	5 (7)	9 (5)	
Chemo+trastuzumab	39 (53)	42 (22)	
Radiotherapy			
50 Gray	46 (62)	107 (57)	0.438
60–66 Gray	28 (38)	81 (43)	
Menopausal status			
Premenopause	37 (50)	93 (49)	0.938
Postmenopause	37 (50)	95 (51)	

Statistically significant p-values are marked in bold. AC: antracycline and cyclophosphamide.

DISCUSSION

In the treatment of breast cancer, the use of NAC is common to decrease the size of the breast mass and permit BCS[8]. The determination of biomarkers before NAC among pCR and non-pCR groups may support the decision to perform BCS at the beginning of treatment[9]. In our study, about 41% of patients underwent BCS in both groups.

In the study by Goorts et al. of 2,046 patients, the most important predictor of pCR was the cT stage[10]. Of the cT1 patients, 31% reached pCR, and among the cT4 patients, 16.5% reached pCR. In this study, positive Cerb-B2, negative ER, and negative PgR were also pCR predictors[10]. For most hormone receptor-positive breast cancers, the pCR rate is low, and chemotherapy does not seem to be helpful[11]. The study by Ohara et al. determined that the luminal A subtype was correlated

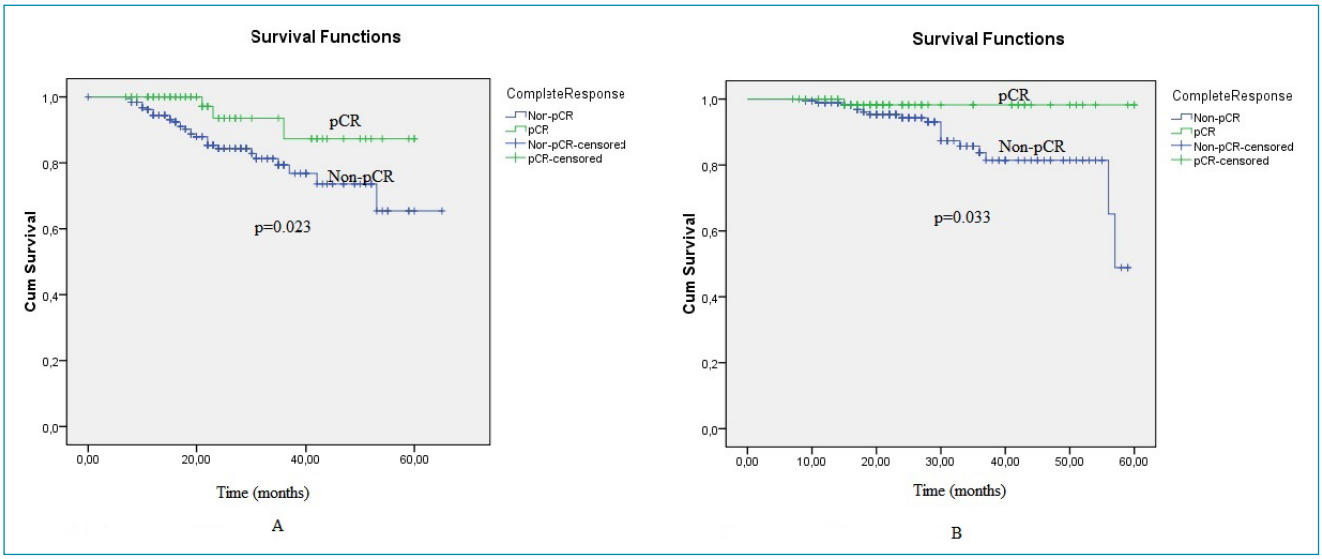

Figure 1. For pathological complete response and non- pathological complete response groups. (A) Disease-free survival. (B) Overall survival.

Table 2. Binary logistic regression analysis for pathological complete response.

	HR	95%CI	p-value
T stages			
T3–4 *versus* T1–2	2.201	1.053–4.602	0.036
LN stages			
LN2–3 *versus* LN0–1	2.074	1.092–3.938	0.026
Estrogen receptor			
Negative *versus* positive	2.012	0.657–6.165	0.221
Progesterone receptor			
Negative *versus* positive	0.629	0.215–1.840	0.398
Cerb-B2 status			
Negative *versus* positive	0.223	0.060–0.825	0.025
Nuclear grade			
Nuclear grade1–2 *versus* NG3	0.314	0.157–0.628	0.001
Ki-67 ratio			
≤20 *versus* >20	0.455	0.173–1.201	0.112
Chemotherapy			
Taxanes+trastuzumab *versus* taxanes	1.361	0.359–5.164	0.651

Statistically significant p-values are marked in bold. LN: lymph nodes.

with the lowest pCR levels[11]. In this study, the logistic regression analysis showed that a low initial clinical stage (T1–T2) and positive Cerb-B2 were statistically significant. Although, ER negativity and PgR negativity are statistically significant for pCR in the univariate analysis, they were not found to be associated with pCR in logistic regression analysis.

In the study by Jarząb et al. of 353 patients treated with NAC, higher rates of pCR were observed in grade three tumors and in patients with Ki67≥20%[12]. In the study by Song et al., tumor localization, nuclear grade, first clinical stage, and number of lymph nodes in the initial diagnosis were identified as important factors affecting OS in the multivariate analysis[13]. In a study by Jain et al., a Ki-67 index >35 and Cerb-B2 positivity were found to be independent predictive factors of pCR[14]. In our study, NG3 positivity and Cerb-B2 positivity before NAC were significant factors affecting pCR in patients, but the Ki-67 ratio was not statistically significant in the logistic regression analysis.

It is known that involved lymph nodes play an important role in the prognosis of patients with breast cancer. Fayanju et al. found that patients who were clinically node-positive at the time of the first diagnosis and who reached pCR had a good prognosis comparable to those who were clinically node-negative at the time of the first diagnosis[15]. The study by Lv et al. showed that before NAC, negative axillary lymph nodes were a positive predictive factor for pCR[16]. OS after NAC is higher with breast-only residual disease compared to residual disease only in the lymph nodes. OS is lowest in both residual diseases. In our study, LN0–1 patients achieved pCR, and OS and DFS were statistically significant.

Achieving pCR is very important for improving OS in patients with nodal involvement in breast cancer. In the study by Silva et al. of 243 patients, the presence of negative hormone receptors was found to be a predictive factor of pCR and associated with shorter OS and DFS. pCR was found to be associated with longer DFS and OS[17]. In several studies where pCR was achieved after NAC, it has been shown that the risk of death decreases and OS increases[9,15,17,18]. In our patients, OS and DFS were statistically significant in the pCR group compared with the non-pCR group.

In some studies, the chemotherapy agents in the NAC protocol have been shown to help achieve pCR[17,19]. In terms of chemotherapy protocols, the addition of trastuzumab to the treatment was not significant in the logistic regression analysis, even if it was significant in the univariate analysis in this study.

The limitations of our study include its small sample size and retrospective design as well as the fact that subgroups such as luminal-A, luminal-B, luminal-B Her-2 positive, triple-negative, and pure her-2 were not included because Ki-67 was unknown in about 11% of patients.

CONCLUSIONS

The NAC response can be used as an early indicator of the prognosis of patients with breast cancer. Today, NAC is also used for patients with early-stage, operable breast cancer because it has been shown in many studies that reaching pCR is associated with positive long-term results. Before NAC, stage T1–T2, LN0–1, Cerb-B2 positivity, and an initial nuclear grade of three were found to be the factors affecting pCR in this study. If we can identify patients who have reached pCR before NAC, we think we can also determine a patient-specific treatment plan at the beginning of treatment.

AUTHORS' CONTRIBUTIONS

OM: Conceptualization, Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. **BI:** Conceptualization, Formal Analysis, Writing – review & editing. **RUG:** Conceptualization, Data curation. **DCT:** Conceptualization, Data curation, Formal Analysis, Investigation. **EA:** Conceptualization, Writing – review & editing. **SBH:** Conceptualization, Data curation, Writing – review & editing. **MBU**: Data curation, Investigation, Writing – review & editing.

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