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Receptor Status Differences in Prognosis for Breast Cancer

Meme Kanseri Prognozunda Reseptör Durumu Farklılıkları

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ABSTRACT

Objective: Breast cancer is a type of cancer that originates in breast tissue cells. It is the most common cancer type in the world after lung cancer. The prognosis of the disease mostly depends on the type and stage of cancer. One of the worst prognoses is seen in a specific type called Triple-negative breast cancer (TNBC), which represents not having any of the three most recognized receptors, namely estrogen, progesterone, and c-erb2 receptors. Our objective was to determine the difference in overall and disease-free survival for breast cancer types categorized by receptor status.

Methods: This is a retrospective matched case-control study with breast cancer patients of two types. A total of 102 patients were divided equally into having TNBC of 51 patients in one arm and triple-positive breast cancer (TPBC) of 51 patients in the other arm. Analyses were run for disease prognostic values and patients' demographic values.

Results: Disease free survival were 63±10.6 months and 93.2±4.9 months in the fifth year for the TNBC and TPBC groups, respectively. (p=0.004) Overall survival was significantly different as 73.9±7.3 months for TNBC and 97.7±2.3 months for TPBC (p=0.002).

Conclusion: TNBC prognosis is worse than that of other breast cancer types. The most important reason is being unable to use hormonal treatment because of the receptor status, and a disease-specific targeted treatment could not have been developed so far. Therefore, it is necessary to identify new molecular targets and develop treatments for them.

Keywords: Breast cancer, estrogen receptor, progesterone receptor, HER2

ÖZ

Amaç: Meme kanseri, meme dokusu hücrelerinden kaynaklanan bir kanser türüdür. Dünyada akciğer kanserinden sonra en sık görülen kanser türüdür. Hastalığın prognozu çoğunlukla kanserin türüne ve evresine bağlıdır. En kötü prognozlardan biri, Triple-negatif meme kanseri (TNBC) adı verilen spesifik bir türde görülür; bu, en çok tanınan üç reseptörden (östrojen, progesteron ve c-erb2 reseptörleri) herhangi birinin bulunmadığını temsil eder. Amacımız, reseptör durumuna göre kategorize edilen meme kanseri türleri için genel ve hastalıksız sağkalımdaki farkı belirlemekti.

Yöntemler: Bu, iki tipteki meme kanseri hastalarıyla yapılan retrospektif, eşleştirilmiş bir olgu kontrol çalışmasıdır. Toplam 102 hasta, bir koldaki 51 hastanın TNBC'ye ve diğer koldaki 51 hastanın Triple-pozitif meme kanserine (TPBC) sahip olması şeklinde eşit olarak bölünmüştür. Analizler hastalığın prognostik değerleri ve hastaların demografik değerleri için yapıldı.

Bulgular: Hastalıksız sağkalım beşinci yılda TNBC ve TPBC grupları için sırasıyla 63±10,6 ay ve 93,2±4,9 ay idi (p=0,004). Genel sağkalım süresi TNBC için 73,9±7,3 ay, TPBC için 97,7±2,3 ay olarak anlamlı farklılık gösterdi (p=0,002).

Sonuç: TNBC prognozu diğer meme kanseri türlerine göre daha kötüdür. En önemli nedeni reseptör durumu nedeniyle hormonal tedavinin uygulanamaması ve bugüne kadar hastalığa özgü hedefe yönelik bir tedavinin geliştirilememiş olmasıdır. Bu nedenle yeni moleküler hedeflerin belirlenmesi ve bunlara yönelik tedavilerin geliştirilmesi gerekmektedir.

Anahtar Sözcükler: Meme kanseri, östrojen reseptörü, progesteron reseptörü, HER2

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INTRODUCTION

Breast cancer is the most common type of cancer among women in Türkiye (1). Prognosis varies because of the biological diversity of the disease, individual differences in the course of the disease, and as a result, the applied treatments differ from each other. Estrogen receptors (ER) are a group of proteins responding to 17β-estradiol with two subtypes as α and β. ERα has been shown to be overexpressed in breast cancer cells (2). Similar to ER, the progesterone receptor (PR) has two isoform, PR-A and PR-B, which reside inside the cells responding to progesterone hormone with steroid structure (3). All cells, including breast epithelial cells, carry two copies of the epithelial growth factor receptor-2 gene (also known as the *HER2* or *c-erbB2* gene). It has been shown that 20-25% of breast cancers carry multiple copies of this gene. HER2-overexpressing tumors are prone to early metastasis and have a poor prognosis (4).

Triple-negative breast cancers (TNBC) are tumors that are negative for estrogen and PRs and HER2. About 10-20% of breast cancer cases are in the TNBC subtype (5). In comparison with hormonal receptor-expressing breast cancer, prognosis is relatively worse and overall survival time. This is because they have a tendency toward visceral metastasis compared with receptor-positive subtypes (6-8). Another reason for the poor prognosis of TNBC is that there is no precise, targeted, proven efficient treatment modality. While there are many agents currently used in cases of ER- and PR-positive breast cancer, new molecules need to be identified in TNBC.

In this study, which was conducted in a single oncology department, our aim was to compare the overall survival parameters of two groups which were consisting of TNBC patients and triple-positive breast cancer patients.

MATERIALS AND METHODS

This study was approved by the Gazi University Clinical Research Ethics Committee (approval number: 254, date: 29.06.2011).

This retrospective matched case-control study was conducted in the Gazi University Faculty of Medicine, Department of Internal Disease with cases followed up at the oncology outpatient clinic from 2001 to 2011. Each study group included 51 patients. Group A comprised TNBC patients, and the other arm (group B) comprised ER, PR, and HER2-positive patients (TPBC). As indicated in the reference study, cases with receptor expression values below 10% for each receptor type and those exhibiting negative immunostaining for HER2 during the initial pathological evaluation were categorized as group A (9). Conversely, cases with receptor expression values exceeding 10% for ER and PR, along with positive immunostaining for HER2, were classified as group B.

The American Joint Committee on Cancer 2003 TNM classification and Scarf-Bloom-Richardson staging system were used for consecutively staging and grading disease. Nottingham Prognostic Index (NPI): 0.2 tumor size (biggest measured diameter) + nodal status [with negative axillary node (1), 1-3 positive node (2), ≥4 positive node (3)] + tumor grade; was used for numeration of prognostic differences for statistical purposes. NPI less than 3.4, between 3.4-5.4 and more than 5.4 were assumed as good, moderate, and bad prognosis, respectively.

Patients were treated according to the up-to-date guidelines for adjuvant, neo-adjuvant, targeted therapy, and radiation therapy according to their initial stages. Patients with metastatic disease and recurrent disease were put on palliative chemotherapy for further treatments.

Statistical Analysis

SPSS program (Released 2008. SPSS Statistics for Windows, version 17.0. Chicago) was used for statistical analyses. Chi-square, Kaplan-Meier survival analysis, and log-rank test were used when appropriate.

RESULTS

Demographics and histopathology: The median age of 102 patients' median age were found as 54.0±12.9 without any significant difference between the two groups (55.1±13.9 and 54.4±12.0 consecutively for group A and B, p=0.772). The characteristics of patients are compared in Table 1.

When histological types were examined, 92.2% (n= 94) of the cases were infiltrative ductal carcinoma, 1% (n=1) were papillary, 1% (n=1) spindle, 2% (n=2) were medullary, 2% (n=2) were mucinous, 1% (n=1) were lobular, and 1% (n=1) were mixed carcinoma. Spindle and medullary breast cancer cases were found to be TNBC, and all papillary, lobular, and mixed types were TPBC.

The mean follow-up time of the cases was 40.97±25.22 months (range; 2-117 months). It was found that 21.6% (n=11) of TNBC cases were diagnosed at the metastatic stage (two of them were diagnosed on initial staging), while 3.9% (n=2) of TPBC cases were detected with metastasis during follow-up. The incidence of metastatic disease progression in group A was higher than that in group B (p=0.008).

Table 1. Characteristic properties of patients

		TNBC-group A	TPBC-group B	Difference (p)
Age (mean)		55.1±13.9	54.4±12.0	0.772
Gender	Female	49	49	NS
	Male	2	2	NS
Menopausal status	Premenopausal	23	23	NS
	Post menopause	26	26	NS
Initial NPI status	Good	4	13	**0.04**
	Moderate	29	25	
	Bad	18	13	
Initial staging	Stage 1	3	14	0.071
	Stage 2	38	26	
	Stage 3	8	11	
	Stage 4	2	0	
Tumor grade (mean)		2.71±0.50	2.2±0.66	**0.000**

Significant differences are marked in bold. NS: Not significant, TNBC: Triple-negative breast cancer, TPBC: Triple-positive breast cancer, NPI: Nottingham Prognostic Index.

When NPI scores were taken into consideration, for the TNBC group, 1 out of 4 patients scored as having a good prognosis, 7 out of 29 patients scored as having a moderate prognosis, and 3 out of 18 patients scored as having a bad prognosis came up with disease recurrence. On the other hand, for the TPBC group, 0 out of 13 patients scored as having a good prognosis, 1 out of 24 patients scored as having a moderate prognosis, and 1 out of 13 patients scored as having a bad prognosis came up with disease recurrence. In comparison of NPI status in connection with disease recurrence, no significant correlation was found between groups A and B (p=0.675 and p=0.60, respectively).

It was observed that 81.8% of recurrences developed in the first 3 years. Disease-free survival rates were 95.9±2.9 months, 86.7±5.1 months, 80.7±6.3 months, 70.9±8.5 and 63±10.6 respectively for the first 5 years of the TNBC group. On the other hand, for TPBC patients, the 5-year disease-free survival was 93.2±4.9 months. When both groups were compared, disease-free survival was observed to be lower in patients with TNBC (Figure 1) (p=0.004).

The overall survival of group A is 94.0±13.4 months, 81.1±5.7 months, 78.6±6.1 months, and 73.9±7.3 months for the first, second, third, and fourth years consecutively. There were deaths recorded for 3 patients in the 1st year, 6 patients in the 2nd year, 1 patient in the 3rd year, and 1 patient in the 4th year. The overall survival of group B patients for 5 years was 97.7±2.3 months. Only one patient lost her life in the 18th month of follow-up. Overall survival of TNBC was significantly lower than that of TPBC (p=0.002) (Figure 2).

DISCUSSION

Breast cancer is a heterogeneous and complex disease about biological behavior, response to treatment, and prognosis. This prognostic information for each individual patient is based on the analysis of biological markers in the primary tumor, including ER, PGR, HER-2 NEU, and Ki67 (10) together with age, tumor size, histological grade, and lymph node involvement. As mentioned before in this article, TPBCs derive benefit from hormonal therapy and targeted therapy, while to target TNBC patients, there are limited therapeutic options. Perou et al. (11) also subdivided TNBC immunohistochemically as basal-like breast cancer, which is mostly studied in the TNBC group. The reason for TNBC to be foregrounded compared with other breast cancer subtypes is that it has a worse prognosis and targeted treatments can not be applied in this breast cancer subtype as a factor contributing to its poor prognosis (11).

Results from numerous studies have shown that TNBC is characterized by a high morphological and core-cytoplasm ratio (12,13). In some observational studies, TNBC was reported to be diagnosed in a younger patient population with an advanced stage of disease and predominantly higher tumor grade (14,15). In our study, we found no significant difference between the two groups according to age. However, the findings matched those of Jack et al. (14) TNBC is more likely diagnosed with advanced stage (p=0.071) and predominantly with higher tumor grade (p=0.001).

Many studies have reported that TNBC patients have poor prognoses compared with other breast cancer subtypes using The NPI, which has also been used for studies conducted later (16). Although our results showed a difference between initial NPI scores, we could not show a significant difference between NPI prognostic criteria scores and disease recurrence for both groups. A possible explanation for this could be the short follow-up period with a lower number of patients.

In a study by Carey et al. (17), it was found that disease-free survival and overall survival of TNBC cases were lower than those of other breast cancer groups. In addition, this patient group had recurrences that were observed mostly in the first 3 years, compared to later periods seen in TPBC patients (17). We observed similar findings as significantly lower disease-free survival in TNBC patients compared with TPBC patients. In addition, it was determined that 81.8% of the relapses observed in group A developed in the first 3 years in accordance with the literature. We also found that overall survival was lower in the TNBC group than in the TPBC group.

Study Limitations

The limitations, including its retrospective design, short follow-up, and lesser number of patients.

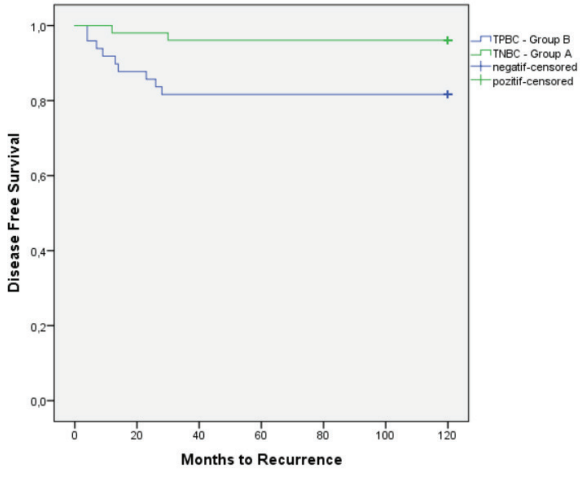

Figure 1. Disease-free survival of the groups.

TNBC: Triple-negative breast cancer, TPBC: Triple-positive breast cancer.

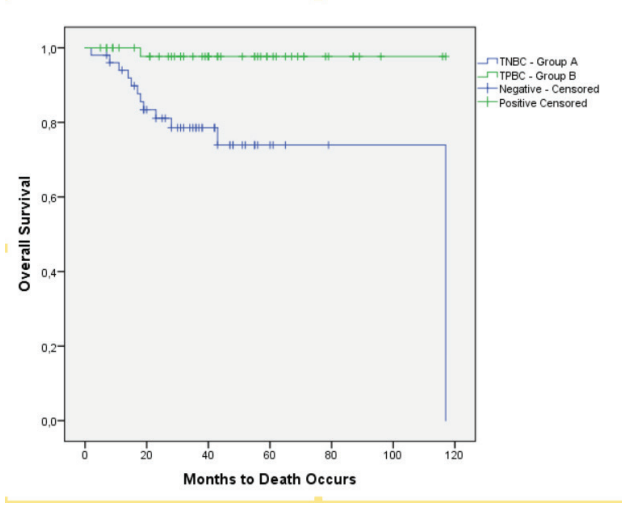

Figure 2. Overall survival analysis of both groups.

TNBC: Triple-negative breast cancer, TPBC: Triple-positive breast cancer.

CONCLUSION

Even with the limitations, including its retrospective design, short follow-up, and lesser number of patients, our results are in accordance with those of published literature and point toward the aggressive nature of TNBC as well as superior outcome of TPBC patients.

Therefore, it is necessary to identify new molecular targets and develop treatments for them.

Ethics

Ethics Committee Approval: This study was approved by the Gazi University Clinical Research Ethics Committee (approval number: 254, date: 29.06.2011).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: D.Y., U.C., Concept: Y.D.B., Design: Y.D.B., U.C., Data Collection or Processing: Y.D.B., D.Y., U.C., Analysis or Interpretation: Y.D.B., D.Y., Literature Search: Y.D.B., Writing: Y.D.B.

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