RESEARCH ARTICLE

Clinicopathologic and Demographic Evaluation of Triple-Negative Breast Cancer Patients among a Turkish Patient Population: a Single Center Experience

Isil Somali[1], Bahar Yakut Ustaoglu[2], Mustafa Oktay Tarhan[3], Seyran Ceri Yigit[4], Lutfiye Demir[3], Hulya Ellidokuz[5], Cigdem Erten[3], Ahmet Alacacioglu[3]

Abstract

Background: To evaluate the clinicopathologic and demographic characteristics of triple-negative breast cancer (TNBC) patients and to determine differences from non-triple-negative cases. Materials and Methods: A detailed review of the medical records of 882 breast cancer (BC) patients was conducted to obtain information regarding age, menopausal status, height and weight at the time of diagnosis, presence of diabetes or hypertension, and pathologic characteristics of the tumor (tumor size, lymph node status, histologic grade, ER status, PR status, HER2 status, p53 mutation). Body mass index (BMI) was calculated and a value of ≥30 was considered as indicative of obesity. Results: 14.9% (n=132) of the patients had TNBC. There was no difference among the patients in terms of median age, comorbid conditions and menopausal status. The proportion of medullary, tubular and mucinous carcinomas was significantly higher (15.9%) in the triple-negative (TN) group, while invasive lobular histology was more frequent (8.2%) among non-triple negative (NTN) cases (p<0.001). Grade 3 (G3) tumors were more frequent in the triple-negative group (p<0.001). The rate of p53 mutation was 44.3% in TN tumors versus 28.2% in the NTN group (p<0.001). The two groups were similar in terms of LN metastasis. In the NTN group, the rate of patients with BMI ≥30 was 53% among postmenopausal patients, while it was 36% among premenopausal women, and the difference was statistically significant (p<0.001). No significant difference was observed in terms of BMI between postmenopausal and premenopausal patients in the TN group (p=0.08). Conclusions: TNBC rates and clinicopathologic characteristics of the Turkish patient population were consistent with the data from Europe and America. However, no relationship between obesity and TNBC was observed in our study. The association between TNBC and obesity needs to be evaluated in a larger patient population.

Keywords: Breast cancer - triple-negative tumors - non-triple-negative breast cancer - BMI

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Introduction

Breast cancer (BC) is a heterogeneous condition, and even the same histologic subtype can exhibit different potentials for recurrence and distant metastasis. Studies evaluating the molecular profile of breast cancer indicate that breast tumors can be classified into five clinically relevant subtypes on the basis of gene expression pattern: Luminal A, luminal B, HER2-overexpressing, basal-like, and unclassified (Perou et al., 2000; Sorlie et al., 2001). Expression of the estrogen receptor (ER), progesterone receptor (PR), and HER2-neu (HER2) alone can be used to roughly differentiate these subtypes (Nielsen et al., 2007). Luminal A and B tumors are ER-positive (+), while HER2-overexpressing tumors are hormone receptor-negative but overexpress HER2 (i.e., ER-/PR-/HER2+). Basal-like and unclassified tumors both have a 'triple-negative' phenotype (i.e., ER-/PR-/HER2-), although approximately 70% of triple-negative tumors are basal-like (Nielsen et al., 2007). Triple-negative breast cancer has been associated with younger age groups and patients presenting with later stages of the disease, and is thought to have a worse prognosis (Bidard et al., 2007). This subgroup accounts for 10-15% of all types of breast cancer (Anders and Carey, 2008). Scientific evidence suggests that women with a higher body mass index (BMI) are at a greater risk of developing breast cancer (Foulkes et al., 2010). This association appears to be driven by distinct molecular mechanisms based on the menopausal status. Indeed, upper body obesity is associated with the risk

*[1]Department of Medical Oncology, [5]Department of Preventive Oncology, Institute of Oncology, Dokuz Eylul University Medical Faculty, [2]Department of Internal Medicine, Tepecik Training and Research Hospital, [3]Department of Medical Oncology, [4]Department of Pathology, Ataturk Training and Research Hospital, Izmir Katip Celebi University, Turkey *For correspondence: demir.lutfiye77@gmail.com*

of developing breast cancer in postmenopausal women, whether or not site-specific adiposity appears to be a major risk factor in premenopausal women (Lahmann et al., 2004; Rose and Vona-Davis, 2010). Unfavorable tumor biology in obese women may also contribute to poorer outcomes. In a population-based study including 1,177 women, obese women under the age of 45 years were found to present higher histologic grades and a higher likelihood of estrogen receptor (ER)-negative tumors (Daling et al., 2001).

In this study, we aimed to investigate the demographic, clinical, and pathological characteristics and BMI among patients with triple-negative breast cancer (TNBC) and to compare them with non-triple-negative breast cancer (NTNBC) in Turkish population.

Materials and Methods

We performed a retrospective analysis of patients with BC treated between 2003 and 2007 at Izmir Ataturk Training and Research Hospital, Department of Medical Oncology. Detailed medical record review was conducted to obtain information regarding age at diagnosis, menopausal status, height and weight at the time of diagnosis, presence of diabetes or hypertension, and pathologic characteristics of the tumor (tumor size, lymph node status, histologic grade, ER status, PR status, HER2 status, p_{53} mutation). For patients with unknown menopausal status, age over 50 years was used as a surrogate of postmenopausal status. Staging was performed according to the version of the American Joint Committee on Cancer (AJCC) cancer Staging Manual applicable at the time of diagnosis. Tumor differentiation or histologic grading was based on Nottingham combined histologic grading system which determines the grade by assessing morphologic features (tubule formation, nuclear pleomorphism, and mitotic count) and provides a classification from grade I to III (low, intermediate, or high grade) (Fitzgibbons et al., 2000).

The performance status (PS) at time of the diagnosis was recorded by using ECOG scale (Oken et al., 1982). The ER and PR analyses were based on an IHC assay, in which a report of >10% cells that with nuclear staining for ER, as well as for PR, was considered a positive result. HER2 was assessed by means of immunohistochemistry (IHC) or FISH. IHC was scored on a qualitative scale from 0 to 3+ based on interpretation of staining intensity, where 0 and 1+ was classified as negative, 2+ as borderline, and 3+ as positive. Immunohistochemically cerbB2 (++) tissues were re-evaluated by FISH analysis; and HER2 gene amplification ratio greater than two was accepted as HER2 positive. The p_{53} mutation was analyzed by means of immunohistochemical (IHC) staining. Nuclear positive staining for mutant p_{53} protein in more than 5% of BC cells was accepted as p_{53} positive. BMI was calculated using the Quetelet Index and categorized according to World Health Organization criteria (De Onis et al., 2007) which classifies BMI into four groups as underweight (BMI<18.5 kg/m^2), normal (BMI 18.5-24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2), and obese (BMI≥30 kg/m^2).

Statistical analysis

Statistical analyses were carried out by using SPPS 15.0 (Statistical Package for the Social Sciences, version 15) statistical program. The mean and median values of the variables were calculated by descriptive analysis. Patient and tumor characteristics were compared according to BMI groups using the t-test, and Pearson's chi-square test was used for categorical variables. A two-sided p value of <0.05 was considered as statistically significant.

Results

Data obtained from 882 patients with BC has been evaluated in the present study. 14.9% (n=132) of these patients were triple-negative (TN) while 85.1% (n=750) were in the non-triple (NT) group. There was no significant difference regarding mean age among patients. Mean age was 24-80 (median: 52.3) in the TN group, and 21-90 (median: 5.34) in the NTN group. There was no difference between the groups regarding the number of patients above the age of 50 years and those under the age of 50 years (p=0.5). According to the accompanying comorbid conditions, there were 12 patients (9.1%) diagnosed with diabetes mellitus in the TN group and 86 patients (11.5%) in the NTN group. There was no significant difference between the two groups (p=0.2). There were 28 patients (21.2%) with hypertension (HT) in the TN group, and 195 (26%) in the non-triple group (p=0.14). The number of patients with coronary artery disease (CAD) was 4 (3%) and 49 (6.5%) in TN group and the non-triple group, respectively. While CAD was more common in the NT group, the difference was statistically significant (p=0.07). Evaluation of the menopausal status showed that there were 46 (42.2%) premenopausal patients in the TN group while the number was 284 (39.3%) in the NTN group. There were 63 (57.8%) postmenopausal patients in the TN group and 438 (60.7%) postmenopausal patients in the NTN group, there was no significant difference between the groups regarding menopausal status (p=0.32) (The demographic characteristics of the patients are presented in Table 1).

Evaluation of the 799 patients with known tumor histology revealed a significant difference. While invasive ductal carcinoma and invasive lobular carcinoma was more common in the NTN group, inflammatory carcinoma and those classified as 'other' (medullary, tubular and mucinous) were more common in the TN group (p<0.001). Data regarding pathological tumor diameter were available for 768 patients. The statistical analysis showed that T1 was significantly more common in the NTN group

Table 1. Demographic Characteristics of the Patients (N=882)

		Triple -negative N=132 (%)	Non-triple -negative N=750 (%)	p value
Median age		52.3	53.4	0.13
Comorbidity	Diabetes mellitus	12 (9.1)	86 (11.5)	0.20
	HT	28 (21.2)	195 (26)	0.14
	CAD	4 (3)	49 (65)	0.07
Menopausal status	Premenopausal	46 (42.2)	284 (39)	0.30
	Postmenopausal	63 (57.8)	438 (60.7)	

Table 2. Tumor Characteristics and Metastasis Status

		TNBC n (%)	NTNBC n (%)	p value
Histology	Inv. Ductal	107 (81.9)	567 (85.0)	0.00
	Inv. Lobular	2 (1.5)	55 (8.2)	
	Inflammatory	2 (1.5)	5 (0.7)	
	Other	21 (15.9)	40 (6.0)	
Tm diameter	T1	19 (15.1)	144 (22.4)	0.01
	T2	85 (67.5)	420 (65.4)	
	T3	13 (10.3)	64 (10.6)	
	T4	9 (7.1)	14 (2.2)	
Grade	G1	8 (6.2)	60 (10.5)	0.00
	G2	69 (53.5)	387 (67.9)	
	G3	52 (40.3)	123 (21.6)	
Lymph node involvement				
	Negative	58 (49.2)	250 (38.1)	0.07
	1-3 LN	28 (23.7)	202 (30.8)	
	> 4	32 (27.1)	204 (31.1)	
p_{53} mut.	Negative	64 (55.7)	435 (71.8)	0.001
	Positive	51 (44.3)	171 (28.2)	

Table 3. Distribution of Patients According to BMI

		BMI 18.5-24.9 kg/m^2	BMI 25-29.9 kg/m^2	BMI≥30 kg/m^2	p value
TN	Premenop. (%)	14 (26.9)	19 (36.5)	19 (36.5)	0.08
	Postmenop. (%)	10 (12.5)	30 (37.5)	40 (50)	
NT	Premenop. (%)	66 (21.7)	129 (42.4)	109 (35.9)	0.00
	Postmenop. (%)	53 (11.9)	154 (34.5)	239 (53.6)	

while T4 significantly more common in the TN group (p=0.01). The evaluation of 699 patients with known tumor histologic grade showed that grade 1 (G1) and grade 2 (G2) tumors were more common in the NTN group while grade 3 (G3) tumors were common in the TN group (p<0.001). There was no significant difference between the two groups regarding lymph node (LN) metastasis. Among the evaluable patients, those negative for LN metastasis were more common in the TN group while patients with 1-3LN metastases and those with >4LN metastases were more common in the NTN group; however, the difference was not significant (p=0.07). Among the 721 patients evaluable for p_{53} mutation, a significantly greater number of p_{53} mutations were found in TN tumors (p_{53} mutation rate was 44.3% in the TN groups vs 28.2% in the NTN group) (p<0.001) (The pathological tumor characteristics of the patients are presented in Table 2).

The evaluation of body mass index and menopausal association revealed no significant difference between premenopausal and postmenopausal patients. However, when TN and NTN patients were evaluated separately, BMI was significantly different between the premenopausal and postmenopausal patients in the NTN group. The rate of patients with BMI≥30 was 53% among postmenopausal women while it was 36% among premenopausal women, and the difference was statistically significant (p<0.001). BMI was higher among postmenopausal women compared to the premenopausal women in the TN group; however, the difference was not statistically different (p=0.08).

Discussion

The present study was designed as a single-center cohort study. The aim of our study was to evaluate demographic and clinicopathologic characteristics of Turkish patients with TN and NTN breast cancer.

The rate of TN breast cancer was 15% among our patients, consistent with the general rate (18%) reported in literature. There was no significant difference between TN and NTN patients regarding mean age (52.3 vs 53.4). In a published, small cohort study in Turkey, mean age was reported as 44 among TN patients and 47.5 among NT patients; however, the difference was not significant (Aksoy et al., 2007). The mean age of patients with TN breast cancer is reported as 61 among American patients, and 50 among Hispanic women (SEER, 2010; Lara-Medina et al., 2011). In a previously published study investigating concomitant conditions, diabetes and arterial hypertension were reported with higher rates among patients with TN breast cancer. In the present study, evaluation of patients with TN and NTN according to comorbid conditions revealed no difference between the two groups.

According to the literature, invasive ductal carcinoma is reported as the most commonly encountered histologic type in TNBC and in all breast cancers (Yutaka and Hirotaka, 2010). On the other hand, invasive lobular carcinoma is reported to account for 5-15% of all breast cancers (Sastre-Garau et al., 1996). The rate of lobular carcinoma has been found to be 1.5% among patients with TNBC, and a previous study by Lin et al. (2012) report this rate as 2%. The rates has been reported as 5.5% in another series (Sastre-Garau, 1996). The other histologic subtypes in TNBC are seen in medullary, tubular, myoepithelial, neuroendocrine, apocrine and adenoid cystic carcinomas (Yutaka and Hirotaka, 2010). In the present study, the rate of invasive ductal carcinoma was significantly higher than that of other histologies in both groups. The rate of invasive lobular carcinoma was 9.7%. It was significantly higher among patients with NTNBC. The rate of medullary, tubular and mucinous carcinomas evaluated as 'other histologies' was significantly higher in cases with TNBC compared to those with NTNBC (15.9 vs 6%).

According to the literature, tumor size expands to greater sizes in TNBC compared to NTNBC (Yutaka and Hirotaka, 2010). Consistent with these data, T4 tumors were significantly more common among cases with TNBC compared to the NTNBC group while T1 tumors were more common in the NTBC group in the present study. There are conflicting reports in literature regarding lymph node involvement in TN breast cancer. While some publications report that lymph node negativity is more common in TNBC (Oakman et al., 2010), some publications report a higher rate of lymph node positivity (Rakha et al., 2008). Currently, the data regarding this aspect remain unclear. While some authors suggest no association, some suggest that lymph node positivity is more common, and lymph node negativity is more common according to some others. Generally, there are publications suggesting that there is no association between increased tumor diameter and lymph node metastasis (Crabb et al., 2008; Rakha et al., 2008). While lymph node negativity was more common in TNBC in the present study, there was no statistically significant difference between the patients groups in terms

of lymph node metastasis. Triple-negative breast cancer is known to be associated with high grade tumors. Similarly, the rate of grade 3 tumors was 40.3% among TN patients, and 21.6% among NTN cases in our study population.

While p_{53} mutation is seen in 30% of all breast cancers, there appears to be a wide range of fluctuation across different subtypes of breast cancer. This rate is approximately 80% in basal-like cancers while it is reported to be less than 15% in luminal breast cancers (Sørlie et al., 2001). In a study evaluating 572 patients, the rate of p_{53} mutation was 26% and 88% in the luminal group and the basal-like group, respectively (Durnay et al., 2013). The rate of p_{53} mutation was 44% and 28% in the TNBC group and the NTNBC group, respectively, and the difference between these two groups were statistically significant (p=0.001).

A few hypotheses have been suggested in an attempt to explain the association between obesity and breast cancer (Pierobon and Frankenfeld, 2013). The first hypothesis is based on the possible stimulation of abnormal growth of ER-positive breast cells caused by the increased estrogen production in adipocytes (Bulun et al., 2012). According to the second hypothesis, if obesity is associated with metabolic syndrome, insulin and insulin-like factor lead to a potent mitogenic activity of epithelial cells (Federico et al., 2007). Epidemiological data shows an association between breast cancer and obesity, and obesity is shown to be a risk factor for breast cancer. However, there are contradicting findings in the literature regarding the association between TNBC and obesity. Some data specify obesity as a risk factor for TNBC (Millikan et al., 2008; Trivers et al., 2009) while some publications suggest that there is no association between the two (Suzuki et al., 2009; Phipps et al., 2011). The association with obesity is clearly seen in receptor-positive breast cancers, particularly among the postmenopausal group (Vona-Davis and Rose, 2007). On the other hand, as there is no receptor expression in TNBC, the association with obesity may be explained by insulin resistance or chronic inflammation in this population (Vona-Davis and Rose, 2007).

The number of patients with BMI>30 was significantly higher in the postmenopausal group of patients with NT breast cancer compared to the premenopausal group in the present study. However, such a difference was not observed in patients with TN breast cancer.

In conclusion, the data and TNBC rates in the Turkish patient population evaluated in this single-centre study were consistent with the data from Europe and America. While the data regarding tumor characteristics were generally consistent with the literature, there was no association between obesity and TNBC in our study. The association between TNBC and obesity may be evaluated in a broader patient population.

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