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ORIGINAL ARTICLE

Excellent clinical outcome of triple-negative breast cancer in younger and older women

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Summary

Purpose: *To compare the histopathological features and survival of triple-negative breast carcinomas (TBNC) in younger and older women.*

Methods: *We documented 312 patients with TBNC between 2008 and 2013. The histopathological and clinical features of women who were 35 years old or younger (N=53) were compared to those of women who were 60 years old and older (N=58). Patients were administered adjuvant or neoadjuvant chemotherapy, and adjuvant radiotherapy.*

Results: *We diagnosed and treated a total of 312 patients with TNBC. The median follow-up was 38 months (mean ±SD:37.36; range: 0.2-383.4). The median age of the younger patients was 32 years (mean ±SD:31.6±3.72; range:19-36) and of older patients 67 years (mean±SD: 68.21±6.78; range:60-84). The tumor size in young patients was larger than in older patients (p=0.001). More comorbid diseases were observed in older patients than in younger ones (p=0.001). There was no difference in the histological grades, lymphovascular invasion, stage and nodal involvement between the two groups. Local / distant metastases were found in 11 (40.7%) patients in the young patient group and in 16 (59.3%) in old patient group (p=0.704). Three (5.4%) patients died from each group. No significant difference in terms of disease-free survival (DFS) and overall survival (OS) (p=0.914, p=0.939, respectively) was noticed.*

Conclusion: *This study showed that older and younger patients with TNBC had similar survival with neoadjuvant and adjuvant chemotherapy and adjuvant radiotherapy, which may be due to similar histopathologic features and intrinsic tumors' activity.*

Key words: *breast cancer, elderly, triple-negative*

Introduction

Breast cancer is the most common malignacy in females with approximately 41% of the cases diagnosed above the age of 65 and 21% above the age of 75 [1,2]. It appears that in older patients 15-18% of breast cancers are triple-negative (TNBC) [1]. Breast cancer at advanced age has been associated with a slightly increased probability of favorable tumor biology, with node-negative, low grade, and positivity of hormone receptors [1,3]. Although TNBCs have a poor prognosis, older patients with TNBC may have a better or equivalent outcome when compared to younger patients. This may be due to the variation in the distribution of biological subtypes within the different age groups [1].

TNBCs have high histological and nuclear grade, high mitotic index, low local relapse rate and increased rate of distant metastases [4]. Relapses and deaths commonly happen within the first 5 years following diagnosis [5,6]. Breast cancer survival at 3 and 10 years is closely related with histological grade, tumor size, and lymph node involvement. After 3 years from diagnosis the influence of the ER-, PR-, and HER2-status decreases, with CK5/6 and/or EGFR positive status becoming the main driving factors [5,7].

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TNBC (ER-negative, PR-negative, and HER-2-negative) has been demonstrated to be relevant to a basal-like phenotype and exhibits more aggressive clinical and pathologic features [8]. About 70-90 % of TN tumors are basal-like tumors. The basal-like phenotype is associated with tumors with medullary-like features and metaplastic elements morphologically [9]. Since TN tumors are a heterogeneous group, TN, basal-like carcinomas and BRCA1-related tumors are not synonymous.

In our study, histopathologic features and survival of TNBC in patients aged 35 years or younger were analyzed and compared with TNBC diagnosed in patients aged 60 years and older. After 5 years from diagnosis retrospective data of these cases are reported and compared to the revelant literature.

Methods

We analyzed 58 (52.3%) tumor specimens from patients aged 60 years or older and 53 (47.7%) tumor samples from patients aged 35 years or younger between 2008 and 2013.

Tumors were graded according to the modified Bloom-Richardson scoring system and staged according to the TNM criteria. In this study, only cases that had no ER-, PR-, and HER2-, were scored as 0 or 1+ according to the guidelines of the American Society of Clinical Oncology (ASCO). The ER and PR statuses were determined by immunohistochemistry (IHC) and the HER-2 status was assessed by IHC or by fluorescence *in situ* hybridization. Patients were treated with various neoadjuvant or adjuvant chemotherapeutic regimens based on anthracyclines, non-anthracyclines, taxanes, platinum and others, and they were also given adjuvant radiotherapy.

Most of the patients over the age of 60 had at least one significant comorbid condition (hypertension, diabetes mellitus, myocardial infarct, congestive heart failure, history of stroke, rheumatological diseases etc). Along with the high incidence of comorbidities, patient preference, performance status and patient access to hospitals were taken into consideration in treatment decisions.

Statistics

SPSS for Windows, version 16.0 was used for all statistical analyses. Pearson's chi-square test was used to compare variables. Kaplan-Meier survival analysis was carried out for DFS and OS and log-rank test was used to examine the statistical significance of the differences observed between the groups. Two-sided p value of <0.05 was considered statistically significant.

Table 1. Distribution of histologic types according to age groups

Histologic type	*Age groups (years)*	
	≤30 N=53	*≥60 N=58*
Invasive ductal	35	42
Basal	5	2
Metaplastic	4	3
Medullary	6	2
Neuroendocrine	1	1
Secretory	1	0
Granular cell	0	1
Pleomorphic	0	1
Adenocystic	0	1
Cribriform	0	1
Lobular	0	2
Mixed	1	0
Apocrine	0	2

Results

We diagnosed and treated a total of 312 patients with TNBC. Median follow-up was 38 months (mean ±SD: 37.36±30.42; range: 0.2-383.4). The median age of the studied patients was 50.1 years (range: 22-84). One hundred and eighty-seven (64.9%) of 312 women underwent mastectomy. One hundred (34.7%) were subjected to breast conserving surgery (BCS) plus adjuvant radiotherapy. Eighteen cases (5.8%) were metastatic at first examination. Two hundred and thirteen (71.2%) of the patients were treated with adjuvant radiotherapy. Two hundred and forty-two (78.1%) of 312 women received adjuvant chemotherapy and 44 (14.2%) received neoadjuvant chemotherapy. Six (1.9%) cases were followed without any treatment. In survival analysis, 61 (19.5%) of the patients relapsed and 17 (5.4%) died during follow-up.

The median age of the younger and older patients who were included in the study were 32 years (mean±SD 31.6±3.72; range:19-36) and 67 years (mean±SD 68.21±6.78; range:60-84), respectively. In the younger group, 35/53 (66 %) tumors were of ductal histological type; Regarding the older patients, 42/58 (72.4%) tumors were of ductal type (Table 1).

The summary of the pathological and clinical features of the tumors that were identified in each patient group can be seen in Table 2. There

Table 2. Baseline characteristics of TNBCs in younger (≤35 years) and older (≥60 years) patients

Characteristics		*Age groups (years)*		*p value*
		≤35 N=53	*≥60 N=58*	
		N (%)	*N (%)*	
Tumor stage	T1	10 (21.3)	18 (33.3)	0.001
	T2	22 (44.7)	31 (57.4)	
	T3	18 (27.7)	3 (5.6)	
	T4	0	1 (1.9)	
	Tx	3 (6.3)	1 (1.8)	
Nodal stage	N0	20 (43.5)	28 (50.9)	0.714
	N1	12 (26.1)	15 (27.3)	
	N2	7 (15.2)	8 (14.5)	
	N3	5 (10.9)	3 (5.5)	
	Nx	2 (4.3)	1 (1.8)	
Grade	1	1 (2.4)	3 (6)	0.339
	2	6 (14.3)	10 (20)	
	3	41 (83.3)	37 (74)	
TNM stage	1	6 (12.8)	13 (22.4)	0.231
	2	10 (14.9)	15 (25.9)	
	3	15 (38.3)	8 (13.8)	
	4	16 (34)	22 (37.9)	
Lymphovascular invasion	No	7 (26.3)	10 (52.6)	0.096
	Yes	18 (73.7)	9 (47.4)	
Radiotherapy	No	11 (23.9)	29 (52.7)	0.001
	Yes	41 (76.1)	26 (47.3)	
Comorbidity	No	43 (74.1)	15 (25.9)	0.001
	Yes	10 (18.9)	43 (81.1)	
Surgery	BCS	18 (40.5)	13 (24.5)	0.218
	MRM	29 (59.5)	37 (69.8)	
	AD	0	1 (1.9)	
	RM	0	2 (3.8)	
	No	43 (74.1)	15 (25.9)	
Treatment	No	1 (1.9)	2 (3.6)	0.860
	Adjuvant	42 (79.2)	43 (76.8)	
	Neoadjuvant	6 (11.3)	5 (8.9)	
	Metastatic	4 (7.6)	6 (10.7)	

MRM: modified radical mastectomy, AD: axillary dissection, RM: radical mastectomy, BCS: breast conserving surgery

was no difference in histological grade, lymphovascular invasion, stage and nodal involvement between the two patient groups. Tumor size in young patients was larger than the in older patients (p=0.001). In the younger group, 11/45 (24.4%) had stage III disease. In the older group 28/56 (50%) had stage I and II disease (p=0.231).

Comorbid diseases in older patients (81.1%) were more prevalent than in younger patients (18.9% ; p=0.001; Table 3).

Local/distant metastases were found in 11 (20.8%) young patients and 16 (27.6%) in old patients (p=0.704). Three (5.7%) patients died from each group. In both groups similar chemotherapy regimens such as anthracycline, non-anthracycline, taxane, and other combinations were used.

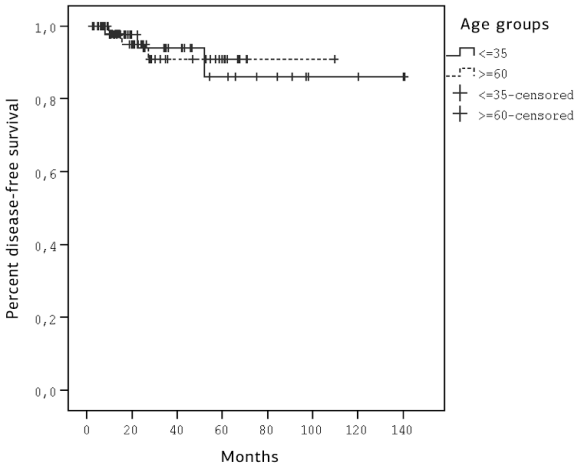

Figure 1. Disease-free survival of younger group (≤ 35 years) and older group (≥ 60 years). Log-rank p=0.941.

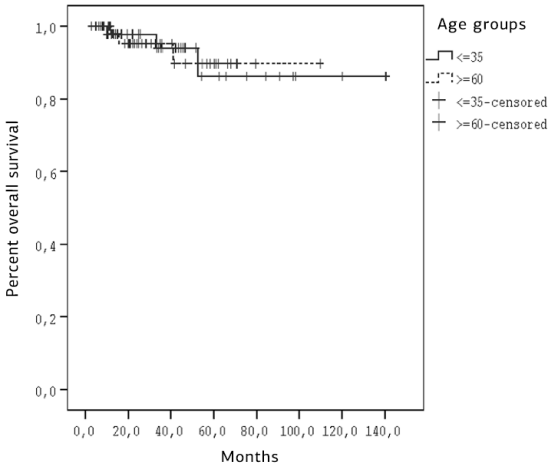

Figure 2. Overall survival of younger group (≤35 years) and older group (≥60 years). Log-rank p=0.939.

There was no significant difference between neoadjuvant and adjuvant chemotherapies administered in both groups (p=0.860), however a significant difference was noticed in the adjuvant radiotherapy between the two groups (p=0.001).

In younger patients DFS rates were 98, 94, and 86% in the first, third, and fifth years, respectively. In older patients, DFS rates were 98, 95 and 89% in the first, third, and fifth years, respectively (p=0.914; Figure 1). In the younger group, the OS rates were 98, 95 and 87% in the first, third, and fifth year, respectively. In the older group, OS rates were 98, 95 and 90% in the first, third, and fifth year, respectively (p=0.939; Figure 2).

Discussion

The management of breast cancer in the elderly has been a topic of debate. There is lack of evidence on the optimal management for this group of patients due to low enrollment in randomized clinical trials. Treatment decisions have been largely based on studies in younger patients that may not be applicable to elderly patients with breast cancer. Breast cancers in elderly women compared to younger ones are histologically less aggressive, smaller, and have a good response to hormonal therapy because of estrogen receptor positive early disease. This favorable biologic profile influences the decision as to whether an elderly patient should be subjected to adjuvant chemotherapy [2].

In our study, tumor size in the older breast cancer group was smaller compared with the younger group (p=0.001). In both groups, no differences in nodal involvement, grade and stage were verified in terms of histopathologic features (p=0.714, p=0.339 and p=0.231, respectively). Thirty-seven (74%) of these tumors were grade III. No lymphovascular invasion was noticed in 10 (52.6%) of the patients and good response to treatment and survival was observed in the older group.

The molecular profiles of TNBC in younger patients are different from the profiles of tumors in older patients [8]. Breast cancer that was detected in younger women is associated with aggressive behavior and poor prognosis [1,8]. TNBC in younger patients were more frequently EGFR-positive (71.6%). Higher levels of EGFR were associated with a more dismal prognosis and lower levels of hormone receptors [8]. EGFR is a predictor of BRCA1 status, and BRCA1-germline mutations are associated with basal-like phenotype and younger patients [8]. In a study, a higher proportion of basal-like phenotype in premenopausal women was found [10]. Several authors have detected high incidence of basal-like carcinomas among TNBC (55.7-75%) [10,11]. These tumors were predominantly high-grade and showed high proliferative activity [10]. For this reason, TN tumors are more likely to hold abnormalities in

Table 3. Patient comorbidities

Comorbidities	*Age groups (years)*	
	≤30 N=53 N (%)	*≥60 N=58 N (%)*
Hypertension	2 (3.8)	9 (15.5)
Asthma	2 (2.6)	0
Diabetes mellitus	0	3 (4.6)
Diabetes mellitus plus hypertension	0	4 (5.3)
Cardiac disease	0	2 (2.1)
Arthritis	0	1 (1.2)
Parkinson and cerebrovascular disease	0	1 (0.6)
Hypercholesterolemia	0	4 (5.1)
No comorbidities	43 (81.1)	33 (57.4)

the p53 and BRCA1 gene, making them quite responsive to taxane and anthracycline-containing regimens.

Retrospective studies have shown that TNBCs had a higher risk of relapse and death , especially in the first 5 years. Hovewer, the rate of late recurrences and death were lower [6,12]. In our study, patients received different chemotherapy regimens.

We did not see a diminishing benefit of chemotherapy as the age of patients increased. These patients were in relatively good health. Similarly, we found beneficial effects with chemotherapy in the two age groups in terms of DFS and OS (1-, 3- and 5-year overall survival rates 98, 94 and 86% in younger patients; and 98, 95 and 90% in older patients, respectively), and excellent prognosis in both groups. Giordano et al. showed that chemotherapy for breast cancer was associated with improved survival among older women with lymph node-positive, ER-negative breast cancer [13].

In one study, in terms of disease specific survival , the entire age group (p=0.006) and the 60-69 years group (p=0.025) demonstrated significant benefit from chemotherapy; however, no statistical significance was observed in both the 55-59 years group and the over 70 years group with negative receptors (p=0.256 and p=1.000, respectively) because of the small number of patients in this group. The 5-year cumulative cancer specific mortality was 18.8± 4.7% for the patients aged 70 years and above [14]. Syed et al. [15] showed that there was no significant difference between the clinical outcome of younger and older patients in respect to recurrence and survival after a 46-month follow up.

In general, comparison of survival shows survival benefit in younger patients. The reasons for the poorer survival rate in the elderly are complex and may be associated with the advanced stage at diagnosis , lower rates of screening, less aggressive treatment due to multiple or severe comorbidities and poorer general health status.

Our study found that younger age was not correlated with shorter DFS and OS. The younger cases were shown to have better survival than in a previous study [16]. It might be related to differences in tumor biology and different histological subtypes rather than chemotherapy regimens. In a study, older patients with TNBC had a lower expression of Ki-67, normal p53 and higher expression of bcl-2 than younger patients. Also these tumors had a high expression of basal cytokeratins 14 and 18 [15]. In our study, most tumors were of non-basal type (90.6%). Infiltrating ductal carcinoma was the most common histologic type in both groups (66.0% in the younger and 72.4% in the older group). The probability of being a BRCA1 mutation carrier and EGFR-positive, stroma-related genes and proliferation gene signatures are low [8]. In the light of the results of the previously mentioned studies, our tumor specimens showed low mitotic index and trabecular growth pattern. Some of these patients had low grade tumors such as adenoid cystic and medullary carcinomas. Some studies reported that the age of breast cancer patients was inversely related to tumor aggressiveness and outcome [8,17]. Menopausal status, tumor stage, nodal involvement, histology, and receptor subtypes (ER-, PR-, HER2-) were the only significant predictors for TNBC patients for being more chemosensitive [17]. Our results were similar in respect to the patterns of treatment. As previously mentioned, no significant differences in cancer stages were observed between the two age groups, however, older patients received less aggressive therapies than younger patients (p=0.231). It is important that genetic subtypes are defined and related to cancer prognosis and to response to treatment. Age might not be an important factor in survival outcomes.

Elkin et al.[18] showed a survival benefit from adjuvant chemotherapy in older women with hormone receptor-negative and node-positive breast cancer. Recent studies showed that chemotherapy for breast cancer was related with improved survival among older patients with positive lymph

nodes [13,18]. In subgroup analysis by age, 13% reduction was found in all-cause mortality among women aged 70 years and older who received adjuvant chemotherapy. Repeat analysis indicated that the benefit of adjuvant chemotherapy did not vary with age in node-positive patients [18].

In conclusion, in patients, especially in older patients, performance status, comorbidities, tumor features , and lymphovascular invasion were significant factors in the decision of chemotherapy administration. TNBC patients 60 years or older with high-risk disease (high grade, node positive) may benefit from adjuvant chemotherapy. Clinical behavior and prognosis of TNBCs were related to histopathological features and treatment options and younger patients with TNBC may have a better outcome with different chemotherapy regimens.

Authors' contributions

NB designed parts of the study, conducted all experiments, collected data and wrote the manuscript. KA coordinated the project and helped in the revision.

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The Ethics Committee of Hacettepe University had no role in the design and conduct of the study, data collection, management, analysis, and interpretation of the data, and preparation, review, or approval of the manuscript.

References

1. Aapro M, Wildiers H. Triple-negative breast cancer in the older population. Ann Oncol 2012;23:52-55.
2. Malik MK, Tartter P, Belfer R. Undertreated breast cancer in the elderly. J Can Epidemiol 2013:1-7.
3. Syed BM, Khyatt WA, Johnston SJ et al. Long-term clinical outcome of oestrogen receptor –positive operable primary breast cancer in older women : a large series from a single centre. Br J Cancer 2011;104:1393-1400.
4. Carey LA, Perou CM, Livasy CA et al. Race, breast cancer subtypes, and survival in the Carolina breast cancer study. JAMA 2006;295:2492-502.
5. Reis-Filho JS, Tutt AN. Triple negative tumours: a critical review. Histopathology 2008;52:108-118.
6. Stockmans G, Deraedt K, Wildiers H, Moerman P, Paridaens R. Triple-negative breast cancer. Curr Opin Oncol 2008;20:614-620.
7. Tischkowitz M, Brunet JS, Begin LR et al. Use of immunohistochemical markers can refine prognosis in triple negative breast cancer. BMC Cancer 2007;7:134.
8. Carvalho FM, Bacchi LM, Santos PP, Bacchi CE. Triple-negative breast carcinomas are a heterogeneous entity that differs between young and old patients. Clinics 2010;65:1033-1036.
9. Toumi Z, Bullen C, Tang AC, Dalal N, Ellenbogen S. Metaplastic breast carcinoma: A case report and systemic review of the literature. Pathol Intern 2011;61:582-588,.
10. Son BH, Dominici LS, Aydogan F et al. Young women with breast cancer in United States and South Korea: Comparison of demographics, pathology and management. APJCP 2015;16:2531-2535.
11. Brot MD, Soares FA, Stiepcich MMA, Curcio VS, Gobbi H. Basal-like breast carcinomas: clinicopathologic and evolutive profile. Rev Assoc Med Bras 2009;55:529-534.
12. Dent R, Trudeau M, Pritchard K et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007;13:4429-4434.
13. Giordano SH, Duan Z, Kuo Y-F, Hortobagyi GN, Goodwin JS. Use and outcomes of adjuvant chemotherapy in older women with breast cancer. J Clin Oncol 2006;18:2750-2756.
14. Jung SP, Lee JE, Lee SK et al. Adjuvant chemotherapy and survival of elderly Korean patients with breast carcinoma. J Breast Cancer 2012;15:296-305.
15. Syed BM, Green AR, Nolan CC, Morgan DL, Ellis IO. Biological characteristic and clinical outcome of triple-negative primary breast cancer in older women-comparison with their younger counterparts. Plos One 2014;9:1-7.
16. Hatem A, Azim JR, Stefan M et al. Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. Clin Cancer Res 2012;18:1341-1351.
17. Kolacinska A, Chalubinska J, Morawiec MB et al. Pathological complete response in younger and older breast cancer patients. Clin Res 2012;2:310-315.
18. Elkin EB, Hurria A, Mitra N, Schrag D, Panageas KS. Adjuvant chemotherapy and survival in older women with hormone receptor-negative breast cancer: Assessing outcome in a population-based, observational cohort. J Clin Oncol 2006;24:2757-2764.