RESEARCH ARTICLE

Androgen Receptor Expression and its Correlation with Other Risk Factors in Triple Negative Breast Cancers: a Report from Western Iran

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Abstract

Background: Androgen receptors (ARs) are expressed in more than 70% of breast cancers (BCs) and have been implicated in BC pathogenesis. Some triple negative (TN)BC tumors express AR and may benefit from AR-targeted therapies. The aim of this study was to evaluate survival and the prevalence of AR expression and its correlation with other risk factors in triple negative BCs in women from Western Iran. Materials and Methods: In a retrospective study between 2009-2015, 41 patients with TNBC were referred to the Private Clinic of Oncology, Kermanshah city, Iran. ER, PR and AR-positive expression was defined as ≥10% nuclear staining and also HER2 (2+), FISH was performed. Nuclear staining was considered representative for Ki67 and P53. The mean follow-up for the patients was 25 months. In this time, 5 patients died and 4 lost to follow-up were censored from survival analysis. Results: The mean age at diagnosis was 46.9 years (range, 24-71 years) and all patients were female. The OS rates for AR-positive and AR-negative patients were 90% and 85.1%, respectively, and the mean OS was 26.3 and 23.2 months. Therefore, there was no significant difference between the two groups (Hazard ratio: 0.580, 95% CI: 0.086-3.893, P=0.575). Conclusions: In TNBC patients, evaluation of AR status may provide additional information on prognosis and treatment. The results of studies showed that the prevalence AR expression may differ in the world and probably ethnicity can be an influencing factor.

Keywords: Breast cancer - triple negative - androgen receptor - Kurdish ethnicity

Asian Pac J Cancer Prev, **17 (7)**, 3321-3324

Introduction

Breast cancer (BC) is a heterogeneous disease with distinct pathological and histological features and can be divided into several subtypes based on the expression of three receptors: estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) (Payandeh et al.,2016a). Triple negative breast cancer (TNBC), characterized as ER-, PR- and human HER2- negative and its prevalence is 10-17% of all breast carcinomas that only partially responsive to chemotherapy and suffers from a lack of clinically established targeted therapies (Payandeh et al.,2015; Anestis et al., 2015). Androgen receptor (AR), a member of the steroid hormone receptor family, is expressed in more than 70% of BCs and has been implicated in BC pathogenesis (Gucalp and Traina, 2010; Shah et al., 2013). Some TNBC tumors express AR) and may benefit from AR-targeted therapies (Barton et al.,2015, McNamara et al.,2013). The significance of AR expression in TNBC is unclear, and published studies so far have been inconclusive (McGhan et al.,2014).

The aim of this study is to evaluate survival and the prevalence of AR expression and its correlation with other risk factors in triple negative BC women: a report from Western Iran.

Materials and Methods

Patients

In a retrospective study, 41 patients with TNBC referred to Private Clinic of Oncloogy, Kermanshah city, Iran, during 2009 to 2015. We checked AR for them and compared other risk factors with it. ER, PR and AR-positive expressions were defined as ≥10% nuclear staining (McGhan et al.,2014; Ogawa et al.,2008; Park et al.,2010). Figure 1 shows immunohistochemical (IHC) staining for AR-positive versus AR-negative. HER2-positive was defined as either HER2 gene amplification by fluorescent in situ hybridization (FISH) or scored as 3+ by IHC and for HER2 (2+), FISH was performed to determine HER2 positivity and HER2 (1+) was negative

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(Payandeh et al.,2016b). Nuclear staining was considered representative for Ki67 and P53. The OS for the patients was from the date of diagnosis until death from any cause. The mean follow-up was 25 months that in this time, 5 patients died and 4 patients lost the follow-up that were censored from survival analysis.

Statistical Analysis

Data analysis was done by SPSS version 19 software (SPSS, Inc., Chicago, USA) that t-test was used for the mean and Chi-square test for other values. The log-rank test was used to evaluate the association between AR expression and survival by GraphPad Prism 5 Software. P-values<0.05 were considered statistically significant.

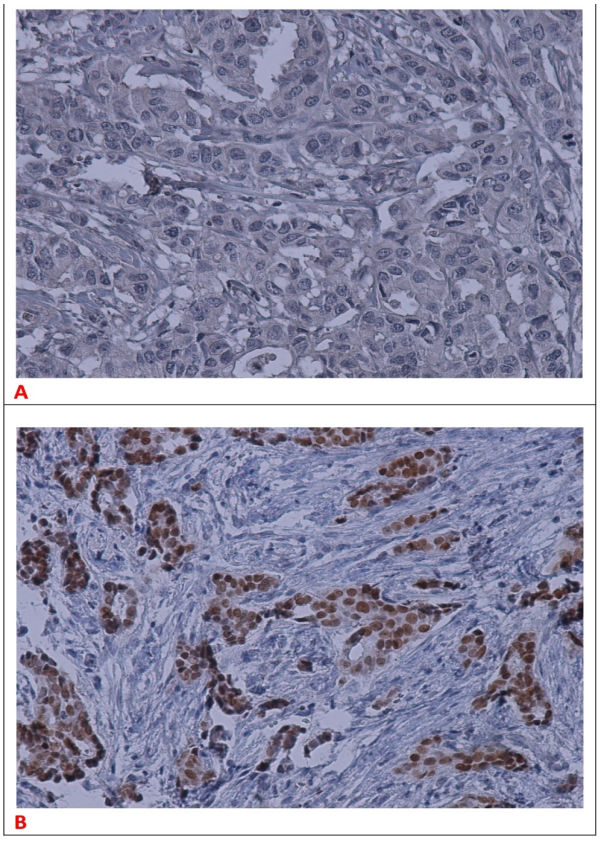

Figure 1. Immunohistochemical Staining for the Androgen Receptor (×400) (A) Androgen receptor-negative, (B) Androgen receptor-positive

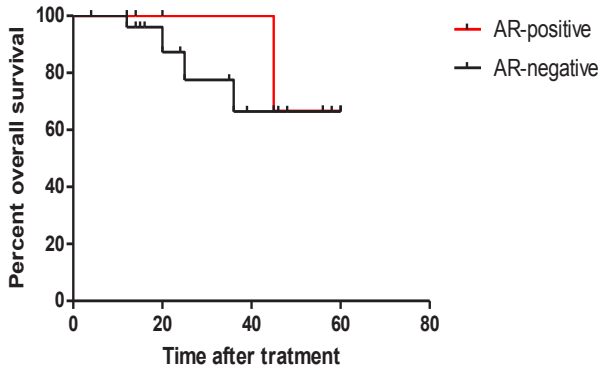

Figure 2. The 5-Year Overall Survival of AR-Positive Versus AR-Negative Triple Negative Breast Cancer Patients

Results

Table 1 shows the baseline variables for TNBC patients. The mean age at diagnosis was 46.9 years(range, 24-71 years) that all patients were female.

The correlation of AR statues with other prognostic factors in TNBC patients has been shown in Table 2. There was significant no correlation between them (P>0.05).

The 5-year OS of AR-positive versus AR-negative

Table 1. The Baseline Characteristics of Triple Negative Breast Cancer Patients(n=41)

Variables	N(%)	Mean±SD	Range
Age, year		46.8±11.4	24-71
Androgen receptor			
Positive	10(24.4)		
Negative	31(75.6)		
Ki-67, %		31.2±22.9	1-70
P53			
Positive	8(34.8)		
Negative	15(65.2)		
Unknown	18		
Laterality			
Right	21(53.8)		
Left	18(46.2)		
Unknown	2		
Metastasis			
Positive	10(24.4)		
Negative	31(75.6)		
Tumor size, cm		3.5±1.8	0.5-8
Type of pathology			
Ductal	36(87.8)		
Lobular	2(4.9)		
Medullary	3(7.3)		
Radiotherapy			
Yes	24(66.7)		
No	12(33.3)		
Unknown	5		
Lymph node metastasis			
Positive	17(44.7)		
Negative	21(55.3)		
Unknown	3		
Grade			
I	2(5.9)		
II	21(61.8)		
III	11(32.4)		
Unknown	7		
Vascular Invasion			
Positive	13(48.1)		
Negative	14(51.9)		
Unknown	14		
Perineural invasion			
Positive	11(44)		
Negative	14(56)		
Unknown	16		
Surgical margin involvement			
Positive	9(26.5)		
Negative	25(73.5)		
Unknown	7		
Stage			
I	2(5.3)		
II	28(73.7)		
III	3(7.9)		
IV	5(13.2)		
Unknown	3		

Table 2. The correlation of AR status with other prognostic factors in triple negative breast cancer patients

Variables	AR-positive N=10	AR-negative N=31	P-value
Age, year			
Mean±SD	47.3±14.1	46.6±10.7	0.871
Ki-67, %			
Mean±SD	28.2±24	32.3±22.9	0.656
P53, n=23			0.596
Positive	3(37.5%)	5(33.3%)	
Negative	5(62.5%)	10(66.7%)	
Laterality, n=39			0.312
Right	6(66.7%)	15(50%)	
Left	3(33.3%)	15(50%)	
Metastasis			0.219
Positive	1(10%)	9(29%)	
Negative	9(90%)	22(71%)	
Tumor size, cm			
Mean±SD	3.1±1.1	3.7±2	0.348
Type of pathology			0.308
Ductal	10(100%)	26(83.9%)	
Lobular	0	2(6.5%)	
Medullary	0	3(9.7)	
Radiotherapy, n=36			0.335
Yes	5(55.6%)	19(70.4%)	
No	4(44.4%)	8(29.6%)	
Lymph node metastasis, n=38			0.49
Positive	5(50%)	12(42.9%)	
Negative	5(50%)	16(57.1%)	
Grade, n=34			0.446
I	0(0%)	2(8%)	
II	7(77.8%)	14(56%)	
III	2(22.2%)	9(36%)	
Vascular Invasion, n=27			0.161
Positive	5(71.4%)	8(40%)	
Negative	2(28.6%)	12(60%)	
Perineural invasion, n=25			0.378
Positive	3(60%)	8(40%)	
Negative	2(40%)	12(60%)	
Surgical margin involvement, n=34			0.105
Positive	4(50%)	5(19.2%)	
Negative	4(50%)	21(80.8%)	
Stage, n=38			0.498
I	0	2(7.1%)	
II	9(90%)	19(67.9%)	
III	0	3(10.7%)	
IV	1(10%)	4(14.3%)	

TNBC patients has been shown in Figure 2. There was no significant difference between two groups (Hazard ratio: 0.580, 95% CI: 0.086-3.893, P=0.575). The OS rate for AR-positive and AR-negative patients were 90% and 85.1%, respectively, and the mean OS for them were 26.3 months and 23.2 months, respectively.

Discussion

In this study, we calculated the prevalence of AR-positive in TNBC patients. Also, we compared survival based on AR status and the correlation with other prognostic factors.

The role of the AR is of particular interest in patients with TNBCs, which represent approximately 25% of all BCs. Emerging evidence suggests that the AR may serve as a therapeutic target for a subset of TNBC (Gucalp and Traina,2010). One study on 94 TNBC patients (McGhan et al.,2014), showed that AR expression was 23%. Niemeier et al. (2010) reported AR expression was in 10 % TNBCs. Other studies, reported that the AR is reportedly expressed in 10-43 % of TNBCs (Luo et al.,2010; He et al.,2012; Lehmann et al.,2011). Sullivan et al. (2014) reported that AR was found in significantly different frequency between African American and Caucasian women with TNBC. In our study, AR was expressed in 24.4% TNBC patients. The results were different and probably ethnicity can effect on the prevalence of AR expression. AR-positive TNBC was more common in older patients and had a higher propensity for LN metastases (McGhan et al.,2014). Luo et al. (2010) found that AR in TNBC correlated significantly with postmenopausal status, lower histological grade, and lack of LN metastasis. Another study, (Choi et al.,2015) showed that positive expression of AR showed significant correlation with older age and lower histological grade.

Rakha et al. (2007) reported that AR negativity was significantly associated with higher histological grade, development of recurrences, and distant metastasis. Among cases with invasive ductal carcinoma, AR expression was significantly related to that of ER and PR, but showed no relation to other parameters, such as age, tumor size, lymph nodes, histological grade, stage, and HER2 status in this surgically treated cohort (Yu et al.,2011). Also, the inverse association between AR and Ki-67, previously reported in invasive ductal carcinoma (McNamara et al.,2015). Our study, showed that there was no significantly different between AR-positive and-negative in age, grade, stage, lymph node metastasis, vascular invasion, perineural invasion, tumor size, Ki-67 status, P53 status, surgical margin involvement, laterality and type of pathology in TNBC women. Therefore, our results are different from other studies that it is probably because the low number of patients in our study.

Hu et al. (2011) reported that women with AR-positive TNBCs had an 83 % increase in overall mortality compared with women with AR-negative tumors. Choi et al. (2015) reported that in univariate and multivariate analyses, AR was significantly a poor prognostic marker for the OS. Another study on multivariate analysis, (6) showed that AR positivity correlated with better OS. A study by Bryan et al. (1984) demonstrated that patients with AR-negative BC had a significant trend toward shorter survival than those with AR-positive tumors (P<0.05), whereas McGhan's study (McGhan et al.,2014) and our study showed that OS was similar between AR-positive and AR-negative patients.

In conclusion, in TNBC patients, evaluation of AR status may provide additional information on prognosis and treatment. The results of studies showed that the prevalence AR expression was different in the world and probably ethnicity can be an effective factor in these differences.

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