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Prognostic Value of Androgen Receptor in Triple Negative Breast Cancer of Iranian Patients in Yazd Region

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ABSTRACT

Background: Triple negative breast cancer (TNBC) is a heterogeneous disease group with a higher recurrence risk and poorer prognosis. In this study, we aimed to investigate the frequency and prognostic value of androgen receptor (AR) expression in tissues of TNBC patients.

Methods: In this study a total of 60 TNBC patients treated between 2011 - 2016 in Shahid Sadoughi and Mortaz Hospital were included and their medical records were analyze. The available paraffin blocks were assessed immunohistochemically to determine AR expression. Tumors with ≥10% nuclear staining were considered AR-positive, while the ones with <10% staining were considered AR-negative. The association between AR expression, and clinical-pathologic characteristics and prognosis in TNBC was analyzed.

Results: The result showed that AR expression in TBNC correlated with high risk of recurrence but no significant correlation with the age, grade, tumor size, lymph node status, type of diagnosis, tumor location, and Ki-67 level was observed. Positive immunoreactivity for AR was observed in 19 out of 60 (11%) specimens. No correlation was observed between the AR expression and the age, grade, tumor size, lymph node status, type of diagnosis, tumor location, and Ki-67 level. The AR-positive patients exhibited high risk of recurrence (P=0.016) and death (P=0.015) in comparison with the AR-negative patients.

Concusions: AR may not be a suitable biomarker and treatment target for the Iranian Yazd patients with TNBC.

Introduction

Triple-negative breast cancer (TNBC) comprises 10-17% of breast cancer.[1] Since TNBC was insensitive to endocrine or target therapy, it was said to have poor prognosis among different molecular subtypes.[2] Many studies have been done on sub-classifying TNBC to find the relation between prognostic and therapeutic factors. In Iran, breast cancer is the most common type of cancer among women comprising 24.4% of all malignancies.[3] Most studies have reported that disease-free survival decrease significantly for patients with TNBC compared with non-TNBC.[3-5] The treatment strategies do not target other tissues in the body and thus, in contrast to other anti-cancer treatments, other organs are not adversely affected. In this regard, immunotherapy has been used as one of the known targeted therapies for breast cancer, in which monoclonal antibodies are used against the hormonal receptors expressed by the breast cancer cells.[6] A study found that tumor grade and stage were relatively higher among AR negative cases compared to AR positive ones, but the difference was not statistically significant in Iranian TBNC patients.[7] There was no significant correlation between AR status and age, tumor size, histopathologic type of tumor, or lymph node involvement. However, AR had a statistically

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significant positive association with a lower tumor grade and lymphovascular invasion in Iranian TBNC.[8] Naimi *et al*. in 2020 claimed that there was not any correlation between the AR expression and grade, stage, lymph node status, and Ki-67 level. The AR-positive patients exhibited higher age and larger tumor size at the time of diagnosis in comparison with the AR-negative patients. Low percentage of Iranian TNBC patients expressed AR and no significant correlation was observed between its expression and most of the clinicopathological parameters.[9] Several studies have explored the potential significance of AR for therapeutic management of both primary and advanced disease, especially in TNBC due to the lack of any other targets. The main aim of the present study was to evaluate the prognostic value of AR expression and its correlation with the clinicopathologic properties of Iranian TNBC patients in Yazd region.

Methods

Breast cancer patients diagnosed with stage I–III TNBC, at Shahid Sadoghi Yazd and Mortaz Hospital between 2011 and 2016, were eligible for this analysis. This retrospective study was conducted at the Pathology Department of Shahid Sadoghi Yazd University of Medical Sciences. Patients were analyzed based on several variables such as: age, pathological parameters (tumor size, grading, necrosis, lymph nodes status, tumor histology, Ki-67, lympho-vascular invasion, androgen receptor expression). Survival analysis was estimated by the Kaplan Meier method. The association between categorical variables was estimated by the Chi square test. The Cox multivariate proportional hazard regression model was used to evaluate the effects of the prognostic factors on survival. Significant differences in probability of surviving between the strata were evaluated by log-rank test. Hazard ratios and 95% confidence intervals (CIs) were estimated from regression coefficients. A significance level of 0.05 was chosen to assess the statistical significance. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software (version19, SPSS, Inc, Chicago, IL).

Immunohistochemistry

The 3–5 mm sections were incubated at 60 ºC (40 min) for de-paraffinization. Then, the samples were immersed in xylene and rehydrated in the decreasing ethanol solutions. To inhibit activation of the

Table 1. Clinicopathological characteristics of TNBC patients

clinicopathological parameters		Information		
Age(years)		Mean 47.18	STD 11.35	Range 25-71
Tumor location	Left Right Unknown	13 21 26		
Tumor size(cm)		Mean 3.58	STD 2.6	Range 0.2-15
Margin involvement	Yes No Unknown	14 27 19		
Lymph node involvement(LNI)	N0(LNI Numbers=0) N1(LNI Numbers<3) N2(LNI Numbers<9) N3(LNI Numbers>9)	41 7 7 5		
Ki67%	<20% <60%&>20% >60% unknown	11 16 14 19		
Recurrence	Yes No	7 53		
Histology	Ductal Medullary Mucinous	50 9 1		
Survival	>(5years) <(5years)	55 5		
Grade	G1 G2 G3	0 24 36		
Ki67	known unknown	41 19		

endogenous peroxidases, the samples were incubated in 0.3% hydrogen peroxide. The antigen retrieval of the samples was done by heating in an 830-W microwave oven (60°C, 15 min) in 10 mmol/L sodium citrate buffer (pH=6.0). Subsequently, the slides were incubated with rabbit anti-human androgen receptor monoclonal antibody (Clone SP107, Master Diagnostica, Granada, Spain) at 4ºC overnight. The primary antibody was replaced with PBS for the negative control. HRP Polymer and DAP Plus Chromogen (Thermo Fisher Scientific, CA) were employed for the detection. Mouse anti-rabbit horseradish peroxidase-conjugated secondary antibody was incubated for 40 min at room temperature. The color was developed using diaminobenzidine (DAB) as a chromogen. The slides were extensively washed with PBS after each step.[6]

Results

Sixty TNBC patients were investigated in this study. Table 1 illustrates the pathological characteristics of the patients.

Table 2. Correlations between AR expression and tumor location, margin, recurrence, histology, survival parameters

Pathological parameters		AR Immunoreactivity (No. of patients (%))			P-Value
		AR-Positive	AR-Negative	Total	
Tumor location	Right	7(33.3%)	14(66.7%)	21(100%)	0.750
	Left	5(38.5%	8(61.5%)	13(100%)	
Margin involvement	Yes	7(36.8%)	12(63.2%)	19(100%)	0.686
	No	7(25.9%)	20(74.1%)	27(100%)	
Recurrence	Yes	5(71.4%)	2(28.6%)	7(100%)	0.016
	No	14(26.4%)	39(73.6%)	53(100%)	
Histology	Ductal	17(34.0%)	33(66.0%)	50(100%)	0.619
	Medullary	2(22.2%)	7(77.8%)	9(100%)	
	Mucinous	0(0.0%)	1(100%)	1(100%)	
Survival	>(5years)	15(27.3%)	40(72.7%)	55(100%)	0.015
	<(5years)	4(80.0%)	1(20.0%)	5(100%)	

Table 3. Association between AR expression and tumor size, lymph node involvement, grade and Ki67 parameters

Clinic pathological parameters		AR Immunoreactivity (No. of patients (%))			P-Value
		AR-Positive	AR-Negative	Total	
Lymph node involvement(LNI)	N0(LNI Numbers=0)	14(34.1%)	27(65.9%)	41(100%)	0.612
	N1(LNI Numbers<3)	1(14.3%)	6(85.7%)	7(100%	
	N02(LNI Numbers<9)	3(42.9%)	4(57.1%)	7(100%)	
	N03(LNI Numbers>9)	1(20.0%)	4(80.0%)	5(100%)	
Tumor size(TS)	TS<3cm	9(33.3%)	18(66.7%)	27(100%)	0.477
	3≤TS≤6	9(36.0%)	16(64.0%)	25(100%)	
	TS>6	1(12.5%)	7(87.5%)	8(100%)	
Grade	G2	9(37.0%)	15(63.0%)	24(100%)	0.428
	G3	10(28.0%)	26(72.0%)	36(100%)	
Ki67%	<20%	2(18.0%)	9(82.0%)	11(100%)	0.460
	<60%&>20%	6(37.0%)	10(63.0%)	16(100%)	
	>60%	3(21.4%)	11(78.6%)	14(100%)	
Age					
	<47	8(25.0%)	24(75.0%)	32(100%)	0.235
	>47	11(39.0%)	17(61.0%)	28(100%)	

Association of AR Expression with pathological Parameters in TNBC Patients

The patients were divided into two groups according to the AR expression (Table 2). Overall, 19 patients (32%) exhibited positive immunostaining for the AR according to the utilized scoring method. Also, 41 patients were negative for AR immunostaining. The correlation between AR expression and pathological parameters was investigated. As illustrated in Table 2, 3, patient's survival with positive expression of AR was less than those with negative expression (P=0.015). Also, AR positivity was associated with a higher risk of disease recurrence (P=0.016). Totally AR expression in TBNC correlated with a high risk of recurrence and death. No significant differences (P>0.05) were detected in age, grade, tumor size, lymph node, type of diagnosis tumor location, and Ki-67 level between these two groups.

Discussion

Androgen receptor is a novel emerging prognostic biomarker in breast cancer. However, there is limited

information about the correlation between the AR expression and pathological features of TNBC patients, especially in the Iranian population. Previous studies found AR to play an effective role in the mammary tumors' development and growth.[10-12] Therefore, AR has gained much attention as a potential target for TNBC treatment.

In this study, androgen receptor expression and its correlation with pathological features of TNBC were investigated. Although, other studies reported a higher percentage of AR-positive TNBC patients, the AR expression was a less common feature in our patients. Among 60 TNBC specimens involved in this study, only 19 (32%) were positive for AR expression. Therefore, it can be concluded that the expression of this receptor in TNBC patients in Iranian population in Yazd regions is lower than that in other regions. AR-positive patients had lower survival rates. Also, the AR expression was correlated with the higher recurrence in comparison with the AR-negative group. However, no significant correlation was observed between other pathological features with AR expression.

In conclusion, optimizing breast cancer therapies to increase cure rates in early stages is necessary in medical oncology. Currently, the studies on treatment strategies for different kinds of cancers are focusing on targeted therapies as specific behavior for destroying the tumor cells. Iranian TNBC patients in Yazd religion exhibited a significantly lower percentage (32%) of AR-positive cases in comparison with other studies in other nationalities. Therefore, AR may not be an appropriate biomarker and potential therapeutic target for the Iranian Yazd patients with TNBC. To validate this finding, we recommend more comprehensive studies with a larger sample size and evaluation of the AR expression with TNBC patients' survival. However, this study confirmed that AR positivity was associated with a higher risk of recurrence and death in agreement with most studies conducted in this regard.

Conflict of Interest

None.

References

1. Reis-Filho J, Tutt A. Triple negative tumours: a critical review. Histopathology. 2008;52(1):108-18.
2. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007;13(15 Pt 1):4429-34.
3. Sadjadi A, Nouraie M, Ghorbani A, Alimohammadian M, Malekzadeh R. Epidemiology of breast cancer in the Islamic Republic of Iran: first results from a population-based cancer registry. EMHJ-Eastern Mediterranean Health Journal, 15 (6), 1426-1431, 2009. 2009.
4. Aghili M, Lashkari M, Farrokhpey AH, Izadi S. Triple-negative breast cancer survival in Iranian patients. Acta Medica Iranica. 2013:560-6.
5. Perez EA. Breast cancer management: opportunities and barriers to an individualized approach. Oncologist. 2011;16 Suppl 1:20-2.
6. Bernard-Marty C, Lebrun F, Awada A, Piccart MJ. Monoclonal antibody-based targeted therapy in breast cancer: current status and future directions. Drugs. 2006;66(12):1577-91.
7. Mohammadizadeh F, Sajadieh S, Sajjadieh H, Kasaei Z. Androgen receptor expression and its relationship with clinicopathological parameters in an Iranian population with invasive breast carcinoma. Adv Biomed Res. 2014;3:132.
8. Jam S, Abdollahi A, Zand S, Khazaeipour Z, Omranipour R, et al. Androgen Receptor Expression in Triple-Negative Breast Cancer. Archives of Breast Cancer. 2019:92-5.
9. Naimi A, Sultan M, Amjadi E, Goli P, Kefayat A. Androgen Receptor Expression and Its Correlation with Clinicopathological Parameters in Iranian Patients with Triple Negative Breast Cancer. Iranian Journal of Pathology. 2020:239-44.
10. Kono M, Fujii T, Lim B, Karuturi MS, Tripathy D, et al. Androgen Receptor Function and Androgen Receptor-Targeted Therapies in Breast Cancer: A Review. JAMA Oncol. 2017;3(9):1266-73.
11. Ricciardelli C, Bianco-Miotto T, Jindal S, Butler LM, Leung S, et al. The magnitude of androgen receptor positivity in breast cancer is critical for reliable prediction of disease outcome. Clinical Cancer Research. 2018;24(10):2328-41.
12. Aleskandarany MA, Abduljabbar R, Ashankyty I, Elmouna A, Jerjees D, et al. Prognostic significance of androgen receptor expression in invasive breast cancer: transcriptomic and protein expression analysis. Breast cancer research and treatment. 2016;159(2):215-27.