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Androgen Receptor Expression in Locally Advanced Breast Cancer Predicts Lack of Pathological Complete Response After Neoadjuvant Treatment

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ABSTRACT

Background: Data regarding the prognostic value of androgen receptor (AR) expression in locally advanced breast cancer (LABC) is limited. We aimed to determine the pathological complete response, defined as ypT0/is and ypN0, in a group of patients with AR-positive breast cancer after preoperative treatment.

Methods: We evaluated immunohistochemical AR expression in 40 patients treated in our referral center. Univariate and multivariate models were used to assess the association between AR expression and pathological complete response (pCR).

Results: AR expression varied from 75% in estrogen receptor-positive tumors to 11.7% in triple-negative tumors ($P < 0.001$). Three patients with AR-positive tumors achieved pCR. In the univariate model, AR expression was significantly associated with the absence of pCR (OR = 0.18; 95% CI, 0.04–0.75; $P = 0.023$). After adjusting for intrinsic breast cancer subtypes, AR-positive tumors had less probability of achieving a pCR compared with AR-negative ones (OR = 12.33; $P = 0.046$).

Conclusions: AR expression was negatively correlated with pCR in our subset of patients with LABC who underwent neoadjuvant chemotherapy.

Introduction

Breast cancer is the leading cause of cancer death in women worldwide. In developing countries, high breast cancer mortality can be attributable to the large proportion of patients with locally advanced breast cancer (LABC) at diagnosis.[1] In Costa Rica, a middle-income country, LABC comprises around one-third of newly diagnosed cases.[2]

For patients with LABC, preoperative chemotherapy provides a reasonable mean for decreasing the tumor burden, assessing in vivo chemosensitivity, and evaluating the possibility of breast- conservation surgery. Furthermore, if these patients achieve a pathological complete response (pCR) after neoadjuvant chemotherapy (defined as ypT0/is ypN0),[3] their long-term outcomes can improve. Pathological complete response has been associated with longer event-free survival and overall survival (OS), especially in triple-negative tumors and HER2-positive breast cancers.[3-5]

Previous studies have demonstrated the prognostic role of androgen receptor (AR) expression in breast cancer patients. Overall, AR-positive tumors are associated with better outcomes and longer OS compared with AR-negative tumors.[6,7] However, few studies have evaluated the predictive value of AR expression regarding pCR in the neoadjuvant setting, and they have yielded conflicting results.[8,9]

In this exploratory study, we aimed to determine

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the association between AR expression and pCR in a subset of patients treated with preoperative chemotherapy for LABC.

Methods

The study protocol was approved by the institutional ethics committee and conducted according to the Helsinki declaration and its modifications.

We prospectively reviewed the clinical records of a sample of 40 patients who underwent neoadjuvant chemotherapy for LABC and who were treated in our referral center (Hospital México, San José, Costa Rica). The Breast Tumor Board decided to offer preoperative systemic treatment to patients with clinical stage IIIA or more (not for stage IV), and to patients in whom the relationship between tumor size and breast size could imply an up-front mastectomy instead of breast-conservation surgery. We excluded the patients who did not complete the preoperative systemic treatment schedule and those who refused surgical treatment. AR expression, as well as the presence or absence of estrogen receptors (ER), progesterone receptors (PR), or human epidermal growth factor receptor 2 (HER2), was determined in formalin-fixed, paraffin-embedded tissues by immunohistochemistry before preoperative treatment (DACO diagnostic Glostrup, Denmark; clone AR441; clone ERSP1; clone PgR636 and polyclonal HER2). Tumors with ≥1% nuclear-stained cells were considered positive for AR, ER, and PR. Immunohistochemical staining for HER2 was scored from 0 to 3+ according to the guidelines for HercepTest™ (DACO, Denmark).[10] HER2 was considered positive when strong (3+) membranous staining was observed, whereas cases with 0 or 1+ were considered negative. In the case of samples scored 2+, a FISH assay was carried out using the PathVysion HER2 DNA Probe Kit (Abbott, Illinois, USA) according to the manufacturer's protocol. Breast tumor intrinsic subtypes were defined according to previous recommendations.[11] Tumor stage was defined according to the criteria set by the Seventh American Joint Committee on Cancer. Histologic grading followed the World Health Organization classification. The pathologist in charge performed the aforementioned histological determinations before preoperative treatment and after surgery. The same pathologist also determined the criteria of pCR in case of absence of invasive tumor in the primary site and absence of metastases in the harvested lymph nodes (ypT0/is ypN0).

Preoperative chemotherapeutic scheme for each patient included one of the following combinations: 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 every 21 days for 4 cycles, followed by weekly paclitaxel 80 mg/m^2 for 12 weeks ($FE_{100}C$ + $_wT$); the same regimen with trastuzumab 6 mg/kg loading dose followed by 4 mg/kg weekly for one year in the case of HER2-positive tumors ($FE_{100}C$ + $_wT$+Tz); epirubicin 100 mg/m^2 and cyclophosphamide 600 mg/m^2 every 15 days for 4 cycles (EC_{dd}); or weekly paclitaxel 80 mg/m^2 for 12 weeks with trastuzumab 6 mg/kg loading dose followed by 4 mg/kg per week for one year ($_wT$+Tz). The surgery was performed by the oncologist surgeon in charge 4 or 10 weeks after the last dose of chemotherapy.

Statistical Analysis

Categorical variables are presented as percentages, and the chi-square test or the Fisher exact test were applied to compare them. The chi-square test for trend was applied to compare AR expression among breast cancer subtypes. A logistic regression was carried out to assess the relationship between AR expression and the probability of achieving a pCR, using breast tumor intrinsic subtypes as covariates. A P value of less than 0.05 was considered statistically significant. Data were analyzed using SPSS for Mac 20.0 (Chicago, IL).

Results

General characteristics of the studied population are presented in Table 1. Overall, 19 patients exhibited AR positivity (47.5%). The AR expression was associated with HER2, ER, and PR co-expression. AR expression varied from 75% in ER-positive tumors to 11.7% in triple-negative tumors (Trend test: $P < 0.001$). Figure 1 shows positive and negative samples for AR immunohistochemistry.

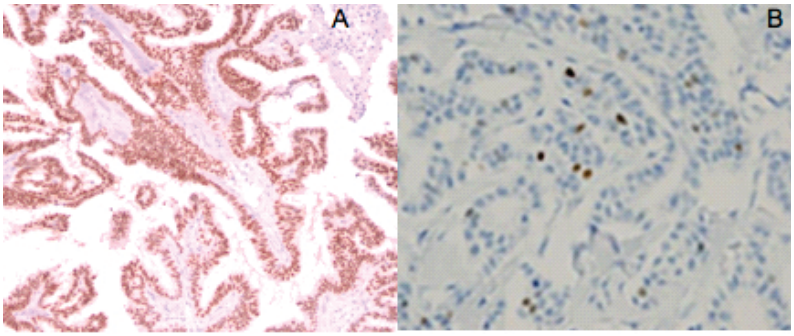

Figure 1. Androgen receptor–positive (A) and receptor–negative (B) breast cancers according to immunohistochemical analysis

Table 1. General characteristics of the studied population

Variable		All patients (N = 40)	AR negative (N = 21)	AR positive (N = 19)	P-value
Age (years, SD)		53.3 ± 10.3	48.22 ± 8.2	54.6 ± 12.3	0.44
Stage					
T					0.72
	T1c	2 (5)	0	2 (10.5)	
	T2	9 (22.5)	4 (19.1)	5 (26.3)	
	T3	24 (60)	13 (61.9)	11 (57.9)	
	T4a	3 (7.5)	2 (9.5)	1 (5.3)	
	T4d	2 (5)	2 (9.5)	0	
N					0.66
	N0	13 (32.5)	4 (19.1)	9	
	N1	18 (45)	8 (38.1)	10	
	N2	7 (17.5)	7 (33.3)	0	
	N3	2 (5)	2 (9.5)	0	
Grade					0.9
	1	2 (5)	0	2 (10.5)	
	2	19 (47.5)	7 (33.3)	12 (63.2)	
	3	19 (47.5)	14 (66.7)	5 (26.3)	
Intrinsic subtype					<0.001
	Luminal A	3 (7.5)	1 (4.7)	2 (10.5)	
	Luminal B	9 (22.5)	2 (9.5)	7 (36.8)	
	HER2-enriched	11 (27.5)	3 (14.3)	8 (42.2)	
	Triple-negative	17 (42.5)	15 (71.5)	2 (10.5)	

** Statistically significant at P < 0.05*

After preoperative chemotherapy, a breast-conservation surgery was possible in 22 patients (55%), and the rest of them underwent for mastectomy. Pathological complete response (ypT0/is ypN0) was achieved in 13 patients (33%). Only 3 patients (15.8%) with AR-positive tumors achieved a pCR. The rate of pCR according to the expression or absence of AR, ER, PR, and HER2 are demonstrated in Table 2. AR-positive tumors had 82% less chance of achieving a pCR compared with patients with AR-negative tumors (OR = 0.18; 95%

After adjusting for each intrinsic breast cancer subtype (Table 2), the absence of AR was independently associated with the probability of achieving a pCR (OR = 0.08; P = 0.046), meaning that the chance of achieving pCR was 92% higher in AR-negative tumors than in AR-positive breast cancer. The Cox-Snell R2 for this model was 0.21, meaning that only 21% of the pCR rate could be explained by this regression model. Figure 2 shows one tumor with pCR and another sample with residual disease.

Table 2. Odds of pathological complete response according to the immunohistochemical expression of breast cancer receptors

Receptor	pCR	Univariate odds ratio (95% CI)	P-value	Adjusted odds ratio** (95% CI)	P-value
AR+ (%)	3 (15.8)	0.18 (0.04-0.75)	0.023	0.08 (0.01-0.97)	0.046
ER+ (%)	2 (13.3)	0.25 (0.05-1.35)	0.09	0.41 (0.17-1.44)	0.44
HER2+ (%)	6 (35.3)	1.17 (0.31-4.44)	0.82	1.33 (0.63-3.77)	0.12
ER-/PR-/HER2- (%)	7 (41.2)	1.87 (0.50-7.19)	0.28	1.83 (0.41-6.72)	0.32

*AR: androgen receptor; ER: estrogen receptor; HER2: human epidermal growth factor type 2; pCR: pathological complete response; PR: progesterone receptor. * Statistically significant at P < 0.05 ** Adjusted for breast cancer intrinsic subtype*

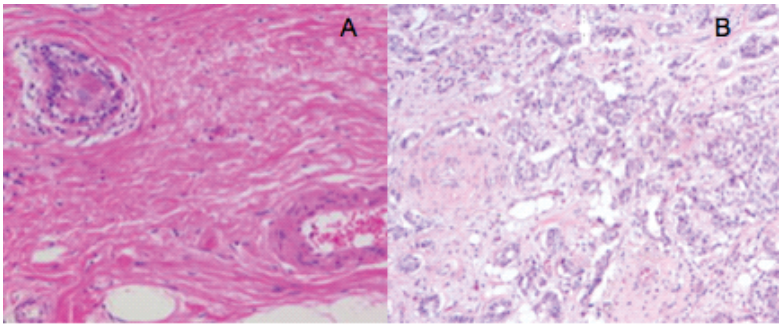

Figure 2. Complete pathological response (A) and residual disease (B) in two breast cancer samples after neoadjuvant chemotherapy

Discussion

Pathological complete response after preoperative chemotherapy is a valuable clinical endpoint because it has been associated with favorable long-term outcomes in patients with LABC,[3] especially for those with HER2 tumors and TNBC. Although some predictive markers have been developed to assess the probability of achieving this endpoint, there is still limited data on the relationship between AR expression and pCR. This possible relationship can be beneficial for improving the understanding and treatment of this particular subset of breast cancer patients.

In this short report, AR expression was positive in 47.5% of the patients, while previous studies have demonstrated a higher AR expression (70–80%). One reason for this inconsistency could be the cancer type, which in our study included mainly HER2-positive and triple-negative tumors. It has been well established that AR expression varies according to the breast cancer intrinsic subtype.[12-14] For example, Collins and colleagues reported the positivity of AR expression in 88% of ER-positive tumors, while only 32% of TNBC were AR-positive.[14] Although the representativeness of ER-positive tumors was low, our data was in accordance with such distribution because the majority of ER-positive tumors also exhibited AR expression.

Our findings demonstrated an inverse association between AR expression and the probability of achieving a pCR. Similar results have been reported by Loibl and colleagues, who showed that AR negativity predicts the odds of achieving pCR. Specifically, these authors reported a pCR rate of 12.8% in AR-positive tumors, while patients with AR-negative breast cancer had a pCR rate of 25.4% ($P < 0.0001$).[9] On the contrary, Masuda and colleagues did not find any significant association between AR expression (determined by immunohistochemistry) and pCR in a cohort of 33 patients with triple-negative breast cancer (TNBC) who underwent preoperative chemotherapy.[15] These divergent results can be attributable to a lower statistical power due to small sample size, as well as the spectrum of patients as Masuda *et al*., only included TNBC patients in their study.[15] It has been demonstrated that patients with triple-negative breast cancer and AR expression have a very low pCR rate in comparison with other TNBC subtypes.[16] Our results are in accordance with this finding as the majority of patients with TNBC who achieved a pCR did not express AR on immunohistochemical analyses.

Having a small sample size and a unicenter design limit generalizability of our findings. Furthermore, information bias might have occurred if patients were misclassified by immunohistochemistry, although we tried to eliminate this bias by choosing only one experienced pathologist to report all samples.

In summary, our findings showed the predictive value of AR expression in patients with LABC undergoing neoadjuvant chemotherapy. However, we must notice that pCR rate can vary according to the presence of some other clinical variables, such as ER and HER2 expression. Further research is warranted to establish the role of androgens in breast cancer patients.

Conflict of interest

The authors declare no conflicts of interest.

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