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Study of Androgen Receptor as a Quadruple Marker in Breast Carcinoma in a Tertiary Care Centre, Maharashtra, India

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ABSTRACT

The second most common tumor in the world is breast tumor. Breast tumors may be defined on the ground absence or presence of Estrogens Receptor (ER), Progesterone Receptor (PR), and overexpression of Human Epidermal Growth Factor Receptor 2 (HER2). The absence of these hormonal receptors (ER, PR, and HER2), define as TNBC (Triple Negative Breast Carcinoma). TNBC is again classified into four subtypes, Basal 1, Basal 2, Luminal, and Mesenchymal Androgen Receptor (LAR). LAR is most perceptive for AR antagonists because it depends on AR signaling pathway. AR performs a major role in breast carcinoma treatment, AR Antagonist is predominantly used in Tamoxifen (SERM) resistant and TNBC. The various subtypes of breast carcinoma show the different pathways of AR action. In this review, we highlight the possible role of AR in prognosis and therapeutic use of AR antagonists.

Keywords: Breast Carcinoma, Estrogens Receptor, Androgen Receptor, Progesterone Receptor, Human Epidermal Growth Factor Receptor 2, Triple Negative Breast Carcinoma

INTRODUCTION

The breast is an epidermal appendage and develops from the apocrine gland of the skin which is functional in lactating females but rudimentary in males. Anatomically it consists of two tissue components: epithelial and stroma. Less than 10% of the total volume of entirely expand female breast (non-lactating) consists of an epithelial component and more than 90% of total breast volume consists of stromal components. Breasts are developing along with the milk line and this milk line expands from the axilla to the groin. In both sex breasts develop similarly up to puberty, post-puberty females' breasts grow under the effect of estrogens, progesterone, and another hormone [1]. Common lesions in the breast are fat necrosis, sub-areolar abscess, duct ectasia, adenoma, fibroadenoma, small duct papilloma, sclerosing adenosis, Paget's disease, breast carcinoma, etc. Breast carcinoma is the second most frequently occurring cancer in women and one of the common causes of cancer-associated fatality [2].

LITERATURE REVIEW

Epidemiology

Breast carcinoma is the second leading carcinoma in the world. In the year 2018 according to the global cancer project and a national report on cancer-related incidence and mortality, approximately 2.089 million cases of breast carcinoma were diagnosed and 6,27,000 cases died due to breast carcinoma world widely in 2018. BC is the most common carcinoma at the moment, share for 11.6% of new cancer cases. In developed countries, per year new cases of breast cancer are higher than in developing countries but the mortality rate is very less compared to developing countries. India has a share of approximately 8% of the worldwide breast cancer burden and facing a very difficult situation because of the higher incidence, approximately 1,62,468 new cases per year in India and 87090 women were die as a result of breast carcinoma in 2018. It becomes now the most common carcinoma in urban India [2].

Risk Factor

The major risk factors are related to:

- Familial breast cancer (germline mutation) i.e. BRCA1 and BRCA2, TP53, CHEK2 mutation, and first-degree relatives are at higher risk of breast carcinoma.
- Sporadic breast carcinoma (Influence by hormone and another environmental risk factor) i.e. menopause, early age menarche, multiparty, lifetime exposure to estrogens, radiation exposure, benign breast disease, carcinoma of contralateral breast or endometrium, breast density, moderate and heavy alcohol consumption increases risk, breast augmentation, obesity, etc. [3].

Histologic Grading System of Breast Carcinoma

The maximum used grading system for breast carcinoma is the Scarff Bloom Richardson grading system modified by Elston Ellis. It helps full to know the degree of differentiation.

This BR grading system depends on the proportion of tubule formation, nuclear pleomorphism, and mitotic count.

All of these parameters are scored from 1 to 3, then the score of all parameters are combined and get a final score which range is 3 to 9. This final score is used for grade determination (Table 1, Table 2, Table 3, and Table 4).

Table 1 Histologic grading system of breast carcinoma (A-Tubule Formation)

Score	Percentage	Tubule formation
1	>75%	Majority of tumor
2	10% to 75%	Moderate of tumor
3	<10%	little or none

Table 2 Histologic grading system of breast carcinoma (B-Nuclear Pleomorphism)

Score	Size of cells	Variation
1	Small, Regular	Uniform nuclei
2	Moderate increase	Moderate variability
3	Marked increase	Marked increase

Table 3 Mitotic activity (In 0.59 mm field diameter or 0.274 mm^2 field area)

Score	Mitotic activity
0 to 9	1
10 to 19	2
>20	3

Table 4 Histologic grading system of breast carcinoma

Score	Grade	Differentiation
3, 4, 5	Grade I (Low Grade)	Well-differentiated
6, 7	Grade II (Intermediated Grade)	Moderately differentiated
8, 9	Grade III (High Grade)	Poorly differentiated

The histological grade is of particular importance for ductal carcinoma of NOS type. However, given the strength of histologic is a prognostic marker. The survival rate gradually declines in Grade- carcinoma up to 70% at 24 years of

age. In Grade III carcinoma, most deaths occurred within 1st ten years after diagnosis, and the survival rate declined up to 45%. Grade - carcinoma patients have a better survival rate as compared to Grade-carcinoma [4,5].

Immunophenotype Classification

To apply immune-histochemical markers, firstly deparaffinized the tissue section by xylene which is fixed in formalin and embedded in paraffin wax. Then they rehydrated in a decline sequence of ethanol. After that tissue section is treated with 0.3% hydrogen peroxide-containing methanol to block any endogenous present peroxidize action. Antigen retrieval (heat mediated) for all staining is done by the pressure cooker method. For immunohistochemical studies, specific antibodies are used on a sequence of tissue sections. In this study, primary antibodies are ER, PR, HER2, and AR by the DAKO staining method.

The immune staining is done by two pathologists and they were blinded for the patient's clinical and pathological characteristics. For antibody scoring, the location of immune-reactivity, immune-reactive intensity, and percentages of immune-reactive cells are determined. For evaluation, every IHC marker appearance should be determined by the mean of each case. Allred scores are used for ER, PR, and AR stains while CK5/6 and CK14 stains consider positive if any membranous or/and cytoplasmic stain is notice [6]. HER2 is also considered positive if strong membrane staining occurs in more than 30% of tumor cells [7-11].

Subtype definitions were as follows (Table 5) [9]:

Table 5 Immuno-phenotype classification of breast carcinoma (Molecular subtype)

Immuno-profile	Luminal A	Luminal B	HER2/neu	Basal-like
ER, PR	ER and/or PR+	ER and/or PR+	ER-, PR-	ER-, PR-
HER2 and others	HER2-	HER2+ or HER2-	HER2+	HER2-
	Low Ki-67 (<14%)	Ki-67=14%		CK5/6 and/or CK14 and/or EGFR+

Immunohistochemistry of Breast Carcinoma

Now a days IHC becomes a common tool for diagnosis and is also used as a prognostic marker in breast carcinoma. It is used to recognize various intracellular and cell surface proteins in the tissue. Different type of carcinoma is the fundamental diagnostic difficulty in the breast. So immunohistochemistry markers may be utilized to differentiate various histological types, molecular subtypes and also helped in the differentiating primary tumor from the metastatic tumor, verifying the tissue of origin, various information about prognosis, helping in the decide treatment modality; predicting response to treatment and evaluation of residual tumor after treatment [12]. Immunohistochemistry markers that are used in breast carcinoma are ER, PR, AR, HER2, Ki67, BRCA1/2, CK5/6, CK14, cyclin D1, cyclin E1, and cyclin Dib [13].

What is Androgen Receptor?

Androgen Receptor (AR) belongs to the superfamily of steroid receptors and is present in various human tissues, among these tissue breast carcinoma has 3rd maximum showing of AR [14,15]. Several studies indicate that overexpression of AR occurs in 70%-90% of breast carcinoma which can play an important role as a prognostic marker and target of the drug in breast carcinoma [16].

AR is a nuclear receptor (type I). It occurs in the cytoplasm, due to the absence of the ligand and is attached with HSP (heat shock protein) and other Chapron. Circulating androgen hormone passively enters through the cell membrane, after that hormone bind to the AR and causes conformational changes in the shape of AR, which disassociates AR from heat shock protein. That causes AR gets activated and forms a dimer. These dimmers move to the nucleus and binding to Androgen Responsive Elements (AREs), causing rectification in DNA transcription. AR dimmers can control gene transcription positively or negatively which causes proliferation, differentiation, angiogenesis, or apoptosis [17].

AR-mediated gene transcription in various subtypes of breast carcinoma: In the ER-positive subtype of breast carcinoma, there is an influential relationship between ER and AR, where these two receptors can regulate transcriptionally each other through hetero-dimerization and binding to the same DNA sequence.

In the ER-negative/HER2 positive subtype of breast carcinoma, the Wnt/β catenin pathway gets activated and facilitates transcriptional activity of AR which promotes tumor growth.

In TNBC, the androgen hormone initiates second messenger signalling cascades which results in a feedback loop and leads to the progression of the tumor [18,19].

Utility of AR in Breast Carcinoma: A study by Fatma Zakaria, et al., shows a correlation between the expression of Androgen receptors and histopathologic grades and found that as tumor grade increased from I to III AR expression decreased from 95% to 76% in Ductal Carcinoma *In Situ* (DCIS) while it decreased 88% to 47% in invasive carcinoma [20].

Also evaluated the value of AR status as a prognostic and predictive marker in TNBC patients and found that Anti-androgen was well tolerated in AR-positive patients with TNBC and associated with over survival and disease-free survival [21].

Yu, et al., also found a negative correlation between androgen receptors and high grades of breast carcinoma [22].

LJ McGhan, et al., concludes that AR is commonly expressed in normal breast tissue and this AR expression decreases with advancement to DCIS and invasive carcinoma. AR-positive TNBC is more common in older patients with a high propensity for lymph node metastasis. AR-positive TNBC may represent a subtype of breast carcinoma with unique characteristics that may be amenable to treatment with Androgen receptor-targeted therapies [23].

CONCLUSION

The percentage of breast carcinoma patients worldwide is 11.6% of all new cases of cancers. Among these, the patients with ER, PR, and HER2 positive are 80%-85% of all breast carcinoma. The standard therapy is used for the treatment of these patients. This standard therapy is not applicable for patients with ER, PR, and HER2 negative. Thus it becomes a necessity to assess the Androgen Receptor sensitivity in such cases, which are 15%-20% of all breast carcinoma, to promote Anti-androgen therapy for better prognosis and survival of the patients, who have not responded to the standard targeted therapy and were left as untreated earlier with being aggressive.

DECLARATIONS

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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