Review

The importance of androgen receptors in breast cancer

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Abstract

Background and aim. Breast cancer (BC) is the most common malignancy among women worldwide, and one of the leading causes of cancer-related deaths in females. For the breast malignant tumors there are numerous targeted therapies, depending on the receptors expressed. Regulating the process of epithelial-mesenchyme transcription, the steroid nuclear receptors are important in invasion and progression of BC cells. Till now, it is known that androgen receptor (AR) is present in about 60-80% of BC cells but, unfortunately, there is no targeted therapy available yet.

Methods. We revised the recent literature that included the AR mechanism of action in patients diagnosed with breast cancer, the preclinical, retrospective and clinical studies and the aspects related to the prognosis of these patients, depending on the molecular subtype.

Results. A total of 12 articles were eligible for this review. AR positivity was assessed using immunohistochemistry. Herein, neither 1 nor 10% cut-points were robustly prognostic. AR was an independent prognostic marker of BC outcome, especially in triple negative BC group.

Conclusion. AR is a potential targeted pathway which can improve the prognostic of AR positive patients with BC. Further preclinical and clinical studies are necessary to clarify the mechanism of action and to establish the drugs which can be used, either alone or in combination.

Keywords: androgen receptor, breast cancer, endocrine therapy

Introduction

Breast cancer (BC) is the most common solid tumor evidenced in women and the principal leading cause of cancer death in the young women population. The treatment of this malignant condition requires a multidisciplinary approach involving surgical oncology, radiation oncology and medical oncology, which has been associated with a reduction in BC mortality. In oncology, the main goals are to increase the curability rate in the adjuvant setting and the survival in the event of metastases. The main research trends are the molecular sub-categorization of BC and the development of new targeted endocrine therapy [1].

It is known that the presence of estrogen receptor (ER) and progesterone receptors (PgR) is associated with better outcome for women with BC, but also with multiple possibilities of therapeutic strategies. Considering that the BC cells can acquire resistance to hormonal therapies, the attention has focused on the role of the androgens and androgen receptor (AR) as a prognostic marker and therapeutic targets [2,3].

Pragmatic clinicians divide breast tumors into three types: those requiring hormonal therapy, those requiring anti-human epidermal growth factor receptor 2 (Her 2) therapy and those requiring chemotherapy. Regardless of the group in which patients fall, special attention must be paid to risk factors, in order to ensure good therapeutic compliance [4-8].

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Diagnosis of BC

BC combines diseases with different evolution and prognosis. The molecular sub-classification is most commonly used, breast tumors being divided according to the presence of hormonal receptors, the protein her2 and the proliferation score Ki-67, in [9,10]:

- Luminal A: ER positive, Her 2 negative, Ki67 low, PgR high
- Luminal B: Her- negative: ER positive, Her 2 negative and either Ki67 high or PgR low
- Her-positive: ER positive, Her 2 positive, any Ki67 high or PgR
- Her 2: Her 2 positive, ER and PgR negative
- Basal like or Triple negative: ER, PgR, Her 2-absent

BC has molecular heterogeneity and although there are multiple molecular targeted therapies, BC mortality remains high. This explains why it is necessary to develop therapeutic strategies including new drugs, especially for triple negative breast cancer (TNBC). In this context, AR is a possible new marker option and a potential new therapeutic target [11,12].

The AR is expressed in more than 50% of BC, but the presence may vary with the antibody used for immunohistochemistry (IHC) and the cut-off of expression. The prognostic role of AR seems to be favourable for BC, but clinical trials are needed to better define AR's prognostic role in different BC subtypes. Those receptors can be stimulated by circulating androgens which are detected physiological during life [13-15].

AR is a member of the steroid hormone family of receptors, together with estrogenic, progesterone and glucocorticoid receptors. It is a steroid hormone with nuclear receptor, which *in vitro* has both inhibitory and stimulatory effects on different BC cell lines growth, probably correlated with the presence or absence of the ER expression. Considering the importance of AR in BC, there are many authors who propose that its identification become routine and be part of the quadruple panel, together with the estrogenic, PgR and human epidermal growth factor receptor 2 [16,17].

AR mechanism of action

In women, the circulating androgens are mainly secreted by the adrenal glands (dehydroepiandrosterone-sulfate - DHEAS, dehydro-androstenedione - DHEA, androstenedione - A4) and by the ovaries (testosterone, A4, DHEA). In the peripheral tissues, such as brain, bone and breast, testosterone, DHT and their metabolites are produced. These hormones play a role in reproductive system, muscle growth and bone loss prevention [18,19].

The concentration of androgen hormones differs during life, the secretion of testosterone decreases in the period of reproductive years and is still present in the menopause period because the androgens ovarian production declines less drastically than the estrogen and progesterone [19].

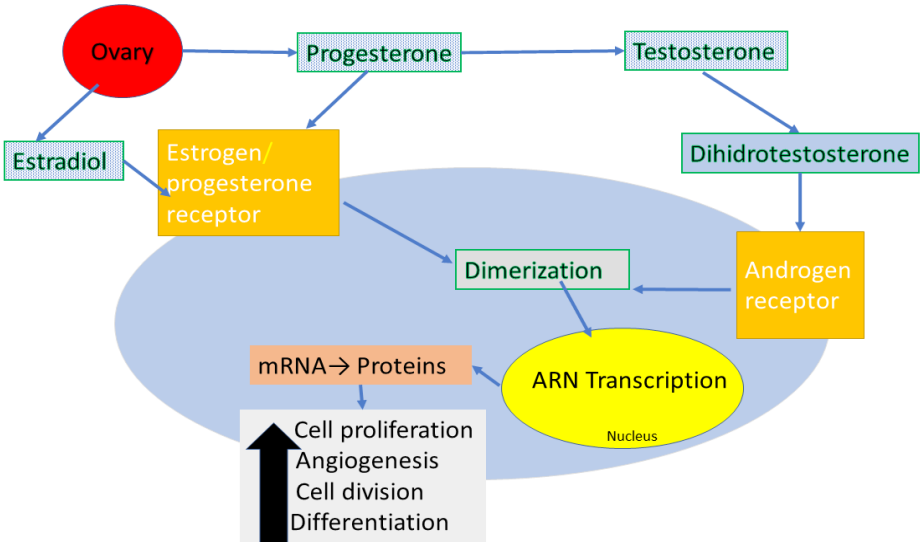

Figure 1. Hormonal receptor activation. Transcriptional/ genomic modality of AR activation: receptor-hormone complex translocates into the nucleus and interacts with co-activators, co-repressor and transcription modulators. As a result, it promotes the transcription of target genes resulting proteins which promotes the cancer cell.

The role of androgens in BC seems to have dual effect, both pro- and anti- tumorigenic. Blood androgens are ligands that bind the membrane AR, which is internalized in the cytoplasm and subsequently transported to the nucleus, where it exerts its effects. The activation of targeted gene transcription leads to mRNA synthesis and subsequent protein synthesis, which finally determine cell proliferation, angiogenesis, cell division and differentiation. Without the ligand, the unbound AR is found in cytoplasm in a complex together with heat shock proteins [20-22].

In vitro data suggest that the presence of the AR on BC cell may play an important role in promoting tumor development (Figure 1). This mechanism was studied in all type of cancer cells. For example, in ER positive cells, high concentrations of the androgen 5α-dehydro-testosterone has shown to cause inhibition of proliferation and cell survival in human BC cell lines expressing both ER and AR. In the same cell lines, activation of AR with dehydrotestosterone leads to a competition between the estrogen and androgen signaling at the nucleus level which one had decreased estrogen- dependent signaling, a similar effect was seen after Tamoxifen administration. Therefore, it is possible that the expression of AR would be associated with reduced cell proliferation and apoptosis [23-25].

On the other hand, the way in which AR acts in tumors with negative ER, PgR and Her2, the triple negative subset, remains incompletely characterized in the area of active research. The preclinical laboratory work, on xenograft murine models and cell lines, suggests that tumor proliferations in this subtype are dependent on the androgen signaling, together with the AR presence. Furthermore, there were some studies, on the same models, with AR- inhibitors or blockers, such as enzalutamide or bicalutamide, with good results. The investigators showed that the androgen signaling, and stimulation of AR is necessary for cell survival and proliferation [26,27].

AR gene is located on the chromosome Xq11-12 and it consists of four domains, an N-terminal domain, a DNA-binding domain, a hinge and a ligand binding domain which acts as a nuclear transcription factor. The effect depends on the presence of the ligand, if this is present, AR translocate into the nucleus, where the DNA-binding domain binds the androgen- responsive elements in DNA and recruits additional co-activators, co-repressors, and transcriptional modulators. In the absence of a ligand, AR attaches to heat shock proteins which are in the cytoplasm [28,29].

In inactive state, the AR is located in the cytoplasm, bound to heat shock proteins. In case of stimulation, the circulating androgens bind to the C-terminal binding domain leading to a conformational change which allows AR dimerization. It translocases into the nucleus and leads to an effect depending on the presence of ER and PgR. In ER positive tumors, AR can promote spread of cancer cell and the resistance to hormonal therapies [23,30,31].

Although most publications discuss AR as a prognostic factor in BC patients, some reports also found an association between AR and therapy response. First, AR was assumed to be a predictive marker for response to endocrine treatment in BC patients. Then, AR was evaluated in ER-positive tumors and a prognostic role of AR could be basically seen in chemo-endocrine treated patients. Additionally, Park et al. described no effect of high AR expression levels on chemotherapy benefit in ER-positive patients, but concluded that patients with low AR expression could be ideal candidates for chemotherapy treatment [3,32-35].

Methods

We searched Pubmed, ScienceDirect, Scopus and Web of Knowledge for articles written in English and published after December 2000. Search terms were androgen receptors, breast cancer, risk and women, alone and in combination. In addition, abstracts from annual meetings of the American Society of Medical Oncology, European Society of Medical Oncology were screened. There was no restriction based on study methodology.

Criteria for the selections of studies

The investigators reviewed every article quoted in this paper and appreciated the possibility to include them in this research according the following inclusion criteria: original and review articles, IHC determination of AR in BC patients, studies that showed the survival outcome after primary treatment, determination of progression free survival or overall survival according to the expression of AR, publication in English. Editorial letters, case reports, animal testing research paper, studies that included men, duplicated articles and non-English articles were excluded. Also, we excluded the articles with no access to the full text of the article.

Results

Figure 2 shows the flow chart of this article. A total of 343 articles were found by using the keywords described above. Finally, after we read the titles and the contents and eliminated the duplicates or the articles that were not related to our concern, we selected and analyzed the rest.

In table I we have summarized the relevant articles for the approached subject and the practical implications resulting in these studies.

AR and primary BC

In a large study conducted by Elebro et al. (n= 910), the authors demonstrated that the AR expression is an important prognostic factor and may have a negative impact the outcome of the patients, especially the AR+/ ER- [36].

Park et al. assessed AR expression using IHC from 413 whole sections and analyzed the tumor characteristic in the presence of AR. They observed that the expression was significant with no elevated preoperative serum cancer antigen 15-3 levels, smaller tumor size, lower tumor grade and hormone receptor-positive and non-triple-negative BC. Regarding the histological type, AR was less present in metaplastic, medullary and mucinous types of carcinomas [37].

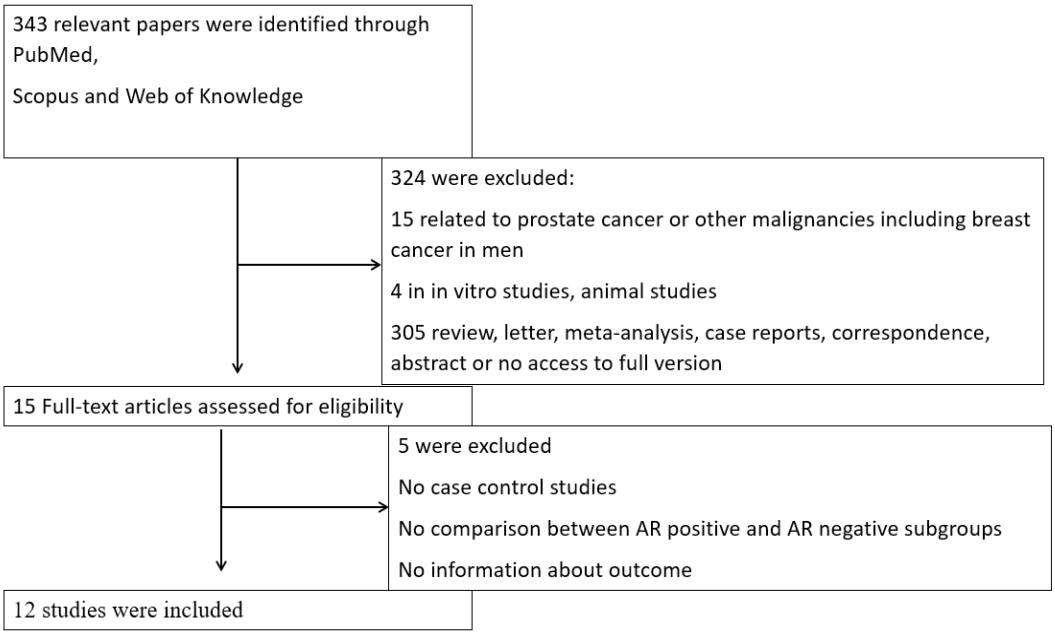

Figure 2. Flow diagram of the study.

Table I. Characteristics of the included studies.

Author/ Year	No. of patients	BC subtype	AR assessment	Concomitant/ experimental treatment	Definition of AR	Prognostic value
Kensler /2019	3021	ER+	IHC	Tamoxifen/ Letrozole	≥1%	Not associated with prognosis
Lehmann /2014	50	TNBC	FFPE sections, DAKO clone AR411	No	>30%	Favorable in combination AR antagonists with PI3K/mTOR inhibitors
Conde /2004	39	CIS, infiltrating carcinoma	IHC+ immunobloting	Tamoxifen	No	Presence of DAX-1 may interfere with endocrine therapy
Guiu /2018	333	TNBC	IHC	No	1%	AR+/ FOXA1+ worse outcome
Dieci /2019	263	TNBC	IHC	Neo/adjuvant treatment	1%	AR+ is associated with worse outcome
Elebro /2017	910	BC	IHC	Yes	>10%	AR+/ER- worse prognosis
Park /2009	413	BC	IHC	No	≥10%	lower tumor burden and favorable differentiation
Gonzalez /2008	83	BC	IHC	No	>10%	AR are represented in breast cancer and are correlated with the expression of some MMPs and TIMP-2.
Caiazza /2016	2091	TNBC	IHC	Enzalutamide	>10%	Provide an alternative treatment for patients with AR-positive TNBC.
Traina /2018	57	TNBC	IHC	Enzalutamide	≥10%	Clinical efficacy, well tolerated
Gucalp /2013	424	ER/PgR-negative	IHC	Bicalutamide	≥10%	Efficacy, minimally toxic androgen blockade
Castellano /2010	953	ER+	IHC	No	10%	Prognostic factor of better outcome

Androgens and hormone receptors positive

The androgens (especially the testosterone) can provide dual effect on breast cell: a proliferative effect mediated by ER and an anti-proliferative effect mediated by AR. Studies showed that high levels of androgens, especially testosterone, increased the risk for BC, regardless of hormonal status. Related to this aspect, the presence of an increased blood concentration of androgenic hormones may lead to tumor proliferation, especially in post- menopausal women [38,39].

The phase III trial by Breast International Group (Trial 1-98) assessed the AR expression among 3021 postmenopausal ER+ BC patients and compared 5 years of tamoxifen or letrozole monotherapy or sequences of two years and three years treatment with one drug and then the other. AR expression neither interferes with the prognosis of BC patients nor can it be categorized as a surrogate marker for individualizing endocrine therapy [40].

It is known that endocrine therapy plays an important role in BC treatment and turning cells into resistant one is an important threshold for physicians. Conde et al. showed that the presence of pattern DAX-1 (dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1) in BC cells may interfere with the intracellular position of both AR and ER and consecutively affect the response to endocrine therapy [41].

AR and cerbB2 positive BC

About half of the breast tumors which express cerbB2 over express AR. The presence of both receptors was associated with a higher frequency of ER and PgR expression, smaller tumor size, earlier clinical stage and lower Ki-67 level compared with AR negativity. Those findings concluded that co expression of both AR and cerbB2 might be associated with less aggressive tumor subtype [37,42].

AR and TNBC

TNBC refers to breast tumors that do not express the genes for hormonal receptors (ER an PgR) and Her2/neu. This type of cancer is more frequent in younger women and people with BC type 1 susceptibility protein (BRCA 1) germline mutation [24,31].

This subtype was also sub classified taking into account the AR, the absence being called quadruple negative. AR expression has been found in 25-75% of TNBC were the AR seems to promote cell proliferation. It is because AR have demonstrated growth action in TNBC cell lines and in vivo models. Taking into account that for this type of tumor the only treatment possibility is with chemotherapy, AR seems to be a potential targeted therapy [43,44].

Clinical studies results related to the influence of AR on the survival of patients with BC are controversial. Retrospectives studies suggested that the AR presence in TBNC is associated with prolonged disease-free survival compared with those with negative AR, with 1% cut-off for IHC. Another study showed that the presence of AR might prolong both overall survival and disease-free survival, in non-metastatic patient, despite the pathological response after neo-adjuvant chemotherapy. In a recent study publish last year, Dieci et al. concluded that AR expression is associated with worsen outcome for TNBC patients [45-48].

PI3K/AKT/mTOR in an important pathway involved in BC development. The androgens up-regulates PTEN transcriptional expression when AR binds to specific cell sites in the PTEN upstream promoter. Subsequently, PTEN restrains PI3K action, which in turn weakens AR activity. In AR+ TNBC, the presence of PIK3CA mutation was higher than the AR negative, therefore dual targeting the AR and PI3K way leads to a synergistic anti- tumor effect [49-53].

In their study, Guiu et al. assessed in a TNBC population both AR and FOXA1 genes and estimated that those tumors are distinct of basal-like and represent 8–12% of all BC. The AR expression was present in 333 patients significant older and with more frequent nodal involvement then the AR negative tumors. The tumors presented lower histologic grades, lobular histology and PIK3CA mutations [54].

AR targeted therapy

Anti-androgen therapy is largely used in prostate cancer although the studies performed until now didn't demonstrate the efficacy of a drug. The first drug used for treatment of metastatic BC was fluoxymesterone and was used in the 1960s. Its use was stopped due to side effects, like hirsutism, hoarseness or alopecia, but also due to incomplete knowledge of the mechanism of action and patient selection [55,56].

After this initial drug, both AR agonists and antagonist were used experimental in clinical studies. For patients with advanced BC, with progression after hormonal therapy or TNBC, first (Bicalutamide) and second generation (Enzalutamide) AR antagonist were used. The first studies were positive, but there are necessary furthermore to demonstrate the efficacy and the tolerability of this drug. Inhibitors of androgen production, like CYP17A1- Abiraterone, were also used in phase 2 clinical trials, alone or in combination with AR antagonists [57-59].

The clinical and preclinical experience had shown that, in TNBC and Her+, AR stimulates proliferation of tumor cells in combination with other effectors like CDK4/6, MEK, and PI3KCA. Those mechanisms command the intracellular circuits leading to invasiveness, survival, proliferation and drug escape. Together with the inhibitors of these pathways, the AR antagonist can be a therapeutic option [60-62].

Also, the new generation anti-androgens have been studied in patients with metastatic BC, like flutamide or enzalutamide. These studies were performed on both cell lines and human sources in phase I or II studies. The first positive phase II trial was conducted by Traina et al.,

enrolled 118 patients, but only 78 were selected to receive enzalutimide and had the AR expression ≥ 10%. Most patients received systemic adjuvant treatment of locally advance BC or for metastases TNBC. The primary end point was the benefit rate at 16 weeks, defined as confirmed complete response (CR) or partial response or stable disease at study week 16. Enzalutamide demonstrated clinical efficacy and was well tolerated. Further studies are needed for use in daily practice [59].

Discussion

Various combined-modality therapies, which are used nowadays such as surgery, endocrine therapy, chemotherapy, targeted therapy, radiation therapy and last but not least, immunotherapy, have improved the outcomes in patients with BC. However, metastasis and recurrence are considered major contributors to treatment failure. Current knowledge of etiopathology, biology, and treatment protocols of breast cancer has benefited from the simultaneous analysis of multiple biomarkers, such as ER, PR, HER2, Ki67, PD-L1 or PIK3CA. These markers are essential in identifying a high-risk phenotype and determining the most efficient therapeutic strategies. However, since breast cancer is a complex and heterogenetic disease, these markers could not cover all disease features. Therefore, it is important to find out new markers with predictive value for survival of patients with breast cancer [63,64].

In the past decades, androgens have been identified to improve the efficacy of hormonal treatment and have been used to treat advanced breast cancer; however, their use has declined with the advent of tamoxifen. Androgens and AR may have some important roles in breast cancer. Some studies have examined and indicated that androgen acts through AR in carcinoma cells and play important roles in biology and clinical behaviour of breast cancer model systems and cell lines [65-67].

The current interest in AR in BC is increasing. AR is a promising primary target for treatment in ER- population and especially in TNBC, were the treatment options are chemotherapy or immunotherapy, more recently. In the TNBC the outcome impact of the presence of those receptors is controversial, with improved or decreased survival. Further studies are necessary to identify which patients may benefit from this therapy [24,68,69].

The roles of androgen and AR in BC and their roles in developing or promoting cancer development are partial unknown. Some of the clinical studies report association between AR expression and prognostic, others no [2,36].

Another aspect studied was the association of AR with other membrane receptor or cell compound like several matrix metalloproteases (MMPs) and their inhibitors (TIMPs). The assessed of both cell compound was high in the positive cells and was correlated with the prognosis [70].

In ER positive BC cell, the AR effect appeared to be dual. AR expression is an independent prognostic factor of better outcome in patients with ER-positive BC, but there are also publications that conclude there is no correlation between the presence of these receptors and neoplastic development [35,71,72].

TNBC has the poorest outcome of the three major subtypes of BC. Numerous studies have aimed to find targeted therapies for this aggressive disease, but so far there are modest result on overall survival and disease-free survival highlight the high- risk of recurrence and metastasis. The discovery of an anti- androgenic therapy has been evaluated in several studies, with promising results, but without use in clinical practice [59,73-75].

Conclusions

This review summarizes the data concerning the mechanism of action and the role of AR in BC, but also the acquired knowledge regarding the anti-androgenic therapy. BC is a heterogeneous disease with a high mortality, despite the numerous therapeutic agents and strategies. AR can be present in 60% of breast tumor cells and can modulate the growth and progression. Together with ER, AR is frequently expressed, suggesting pivotal expression in progression of BC. In ER positive patients, the AR can either inhibit or promote the BC cell growth, while it predominantly stimulates the cell proliferation in ER negative BC patients. The effect can be done in an independent manner or in combination with other targeted therapy.

In TNBC the data showed that AR expression seemed to be a favorable prognostic factor. Routine assessment of AR and also the cut-off may help identifying patients who will benefit from AR therapy. Especially in this particular subtype, AR is an emerging and promising therapeutic target, both because the lack of therapeutic possibilities and the bad prognostic.

To conclude, increased understanding of the AR role, which can benefit from AR targeted therapy and what drugs are effective for AR positive tumor, are some aspects which may potentially prove to be treatment options for BC patients.

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