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INVITED COMMENTARY

Role of Androgen Receptors as a Prognostic and Predictive Biomarker in Triple-Negative Breast Cancer

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Abstract Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer, and there are currently no targeted agents approved for its treatment. It is increasingly being realized that this entity by itself is quite heterogenous and the use of biomarkers can help in better characterization of its prognosis and development of appropriate therapeutic strategies. Recently, androgen receptors (AR) and their signaling cascade have been increasingly evaluated in TNBC. Their exact role in the pathogenesis and progression of the disease is still obscured. Drugs like bicalutamide and enzalutamide have shown some activity in this subtype. This review will focus on the available evidence supporting the role of androgen receptors in the prognosis of TNBC and current status of therapies targeting these receptors.

Keywords TNBC · Triple-negative breast cancer · AR · Androgen receptor · Breast cancer · Breast cancer subtype · Therapeutic strategies · Bicalutamide · Enzalutamide · Biomarkers · Review · Commentary

Introduction

Triple-negative breast cancer (TNBC) is a heterogenous group consisting of tumors characterized by the absence of estrogen receptor (ER) and progesterone receptor (PR) expression as well as HER-2 overexpression and/or amplification [1]. As compared to their counterparts (ER/PR and/or Her-2 positive), treating this subtype can be utterly frustrating in the absence of any targeted therapy available which is further compounded by the aggressive nature of disease. As molecular pathways of triple-negative groups are unraveling, more avenues of prognostication and treatment are opening up.

Androgen receptors (AR), a member of the steroid superfamily, are present in 70–90 % of all breast cancers and up to one third of TNBCs [2]. Recently, AR has emerged as a potential therapeutic target in breast cancer, particularly in the triple-negative subset. This newly found interest in therapies for this pathway arises from both elucidation of molecular subtypes of triple-negative breast cancer and parallel successful development of next-generation AR-directed therapies in prostate cancer. This review aims at summarizing preclinical and clinical data for AR in triple-negative breast cancer as a predictive and prognostic biomarker and ongoing research in this field.

Androgen Receptors

The gene for the AR is present on chromosome Xq 11–12. Androgen receptors are formed by a single polypeptide with four domains with different functions. Lehman et al. by gene expression (GE) analysis subdivided TNBC into at least six distinct molecular subtypes, including two basal-like (BL1 and BL2), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem-like (MSL), and a luminal androgen receptor (LAR) subtype [3]. In their GE analysis of tumors from 21 studies, the prevalence of the LAR tumors was 11 % (62 of 587) of TNBCs, while it constituted only 2 % (62 of 3247) of all breast cancers. They also demonstrated that in LAR tumors, AR mRNA was highly expressed, on average at

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ninefold greater than all other subtypes. Furthermore, the tumors within the LAR group also expressed numerous downstream AR targets and coactivators (*DHCR24*, *ALCAM*, *FASN*, *FKBP5*, *APOD*, *PIP*, *SPDEF*, and *CLDN8*). Other than this, the percentage of tumor cells scored with nuclear AR staining and the intensity of staining were significantly higher in the LAR subtype [3].

Role of Androgen Receptors in the Prognosis of Triple-Negative Breast Cancer

The relation of androgen receptors to overall outcome in TNBC is not very clear. Moreover, TNBC being the less common subtype of breast cancer, most of the studies have limitations of small sample sizes. Studies that have focussed on prognosis can be divided into two types: those done in ER-negative disease irrespective of Her-2 status and those specifically in the TNBC group. Studies that have not taken into account Her-2 status would not be very relevant for discussion here as a substantial amount of ER-negative tumors would be Her-2 positive which is an important prognostic factor and might have different interactions with AR as compared to TNBC [4, 5].

In various studies performed to date, the outcome in triple-negative breast cancers with androgen receptors has varied from poor prognosis to no effect on prognosis to good effect on prognosis (Table 1). Mc Nemara et al. showed that only AR expression in tumor cells did not show any significant effect on prognosis of TNBC patients, but the presence of an androgen-synthesizing pathway in addition to AR caused decreased cell proliferation, thus indicating that not only the receptor's expression but also its ligands are the factors governing tumor growth [6]. In a neoadjuvant setting, Yu et al. studied the subgroup of TNBC having residual disease after neoadjuvant chemotherapy. They found that the patients who did not relapse were characterized by high expression of "luminal-like" genes such as AR and GATA 3 in residual tumor. These results suggest that in this context, AR positivity might represent a good prognostic factor [7].

This difference in prognosis could also be attributed to different methodologies for doing androgen receptor analysis, different cutoffs (1–10 %), and lack of any guidelines for androgen receptors. Since most studies showed a trend toward higher age for this subset, there is a possibility that some of the older patients might have received undertreatment. Hence, future studies evaluating prognosis must take this fact into account.

Preclinical Research for Predictive Value of Androgen Receptors in TNBC

It seems logical that anti-androgens will act in the LAR subtype as it is enriched in AR. Lehman et al. showed that LAR cell lines were sensitive to bicalutamide and the Hsp90 inhibitor 17-dimethylaminoethylamino-17-demethoxy-geldanamycin (17-DMAG) as compared to other subtypes,

Table 1 Studies evaluating the prognostic significance of AR in breast cancer

Author	Number of patients	Number of patients with AR positivity	Technique for AR measurement	Definition of AR positivity	Outcome in AR-positive patients	Comments
He et al. [11]	287	74	IHC	5 %	AR expression good prognosis for DFS	AR negative had higher proportion of lymph node metastasis
Mc Ghan LJ et al. [12]	94	22	IHC	>10 %	Similar locoregional recurrence, disease-free survival, and overall survival	Associated with older age and lymph node metastasis
Choi JE [13]	492	87	IHC	>1 %	Poor overall survival	Significant correlation with older age, apocrine histology, and lower histologic grade
Pistelli et al. [14]	18	15	IHC	>10 %	No effect on disease-free survival and overall survival	Positive AR was inversely correlated with a higher Ki-67 and lympho-vascular invasion
Thike et al. [15]	699	265	IHC	>1 %	DFS was significantly better in AR positive with a trend for improved overall survival	Androgen receptor expression was inversely associated with histologic grade and mitotic score

suggesting that LAR tumors are driven by AR signaling and this pathway can be targeted to improve outcomes in this subset [3]. Most of the preclinical research for androgen receptors thus focussed on this. However, recently, Barton et al. demonstrated that even the non-LAR type of TNBC is critically dependent upon the androgen pathway by using enzalutamide and androgen receptor knockdown in in vitro and in vivo models [8]. In four TNBC lines (SUM159PT, HCC1806, BT549, and MDA-MB-231), representing three non-LAR TNBC molecular subtypes (mesenchymal-like, mesenchymal stem-like, and basal-like), AR inhibition significantly reduced baseline proliferation, anchorage-independent growth, migration, and invasion and increased apoptosis. In a xenograft model of mice, androgen receptor inhibition in cell lines SUM159PT-TGL (representing MSL) and HCC1806-TGL (representing BL2) caused decreased viability and increased necrosis and apoptosis.

Other than androgen receptor targeting, LAR cell lines have also been shown to be sensitive to PI3k inhibitors [3]. Furthermore, this sensitivity correlated with PIK3CA mutation [3]. These finding suggests that dual inhibition of AR and the PI3K/mTOR pathway may be synergistic and thus clinically beneficial. Trials (NCT02457910) are ongoing to explore this strategy as shown in Table 2.

Clinical Research with Predictive Value

Gucalp et al. conducted a phase II trial of bicalutamide (150 mg/day) in ER−/PR−/AR+ metastatic breast cancer. The frequency of AR positivity was defined by >10 % nuclear staining by immunohistochemistry and was only 12 % (n=51, out of 424 patients screened). They demonstrated a clinical benefit rate of 19 %, suggesting that AR antagonists may be an effective targeted therapy for some patients with AR-positive TNBC [9]. However, this drug did not live up to its expectations as expected from in vitro study and comparing it with estrogen receptor analogy. The reason for the limited benefit of bicalutamide could be many—including its partial agonistic activity and low affinity to the androgen receptors. Perhaps drugs like enzalutamide could have ameliorated this problem as it has a sixfold higher affinity to AR relative to bicalutamide and it has a pure antagonist property. Furthermore, it targets multiple steps in the AR signaling pathway, including inhibition of AR nuclear translocation, DNA binding, and co-activator recruitment of the ligand–receptor complex.

Recently, Tiffany et al. presented data in ASCO 2015 for enzalutamide use in TNBC. The primary endpoint was clinical benefit [complete response (CR), partial response (PR), or stable disease (SD)] at 16 weeks (CBR16) in “evaluable” pts defined as having both AR IHC ≥10 % and a response assessment done [10]. Besides, an androgen-related gene signature (Dx+) was created and clinical response was also correlated with that. Of the 75 evaluable patients, CBR at 16 weeks was 35 % and CBR at 24 weeks was 29 %. Furthermore, in patients with androgen receptor positivity, Dx+ patients showed better responses as compared to Dx− ones [10].

Practical problems in conducting these studies have been the lack of standardization of biomarkers, rarity of these subsets, slow accrual, and difficulty to assess responses by RECIST criteria.

Table 2 Ongoing trials targeting AR in triple-negative breast cancer

Study, Clinical Trials.gov.	Clinical trial	Agents	Phase	Current status
NCT02457910	A phase Ib/II trial of taselisib (GDC-0032), a PI3K inhibitor, in combination with enzalutamide in patients with androgen receptor-positive TNBC	Enzalutamide and taselisib	Ib/II	Currently recruiting
NCT01842321	A phase II trial evaluating the activity of abiraterone acetate plus prednisone in patients with a molecular apocrine HER-2-negative locally advanced or metastatic breast cancer	Abiraterone acetate and prednisolone	II	Ongoing but not recruiting
NCT02353988	Bicalutamide in treating patients with AR-positive metastatic TNBC	Bicalutamide	II	Not yet recruiting
NCT02368691	Open-label, multicenter, multinational study investigating the efficacy and safety of GTx-024 on advanced, androgen receptor-positive TNBC	GTx-024	II	Currently recruiting participants
NCT00468715	Bicalutamide for the treatment of androgen receptor-positive, estrogen receptor-negative, progesterone receptor-negative (ER(−)/PR(−)) metastatic breast cancer patients: a phase II feasibility study	Bicalutamide	II	Ongoing but not recruiting participants

Conclusions

Androgen receptors do have a role to play in triple-negative breast cancer, though further trials are needed to define the optimal use. More studies with larger sample sizes should be done with uniform methodologies and similar cutoff for androgen receptors to be comparable to each other. Furthermore, studies should be biomarker driven so that the small subset of AR-positive triple-negative breast cancer which might respond to AR-directed therapy can be better delineated. Most of the studies discussed here highlight the difficulty in conducting trials in the era of precision medicine targeting a rare subset of common diseases. Besides, it remains to be explored whether it is prudent to target androgen receptors alone or in combination with other therapies.

Compliance with Ethics Guidelines

Conflict of Interest Sameer Rastogi and Bhawna Sirohi declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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