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Mini-review

Androgen receptor and antiandrogen therapy in male breast cancer

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ABSTRACT

Cancers arising in the male breast are uncommon. Male breast cancer is a hormone-driven disease that often expresses the estrogen receptor, and antiestrogen therapy represents the mainstay of treatment. Paradoxically, the advent of a wave of antiestrogens eclipsed the therapeutic potential of alternative therapeutic options. At the beginning of the hormonal therapy era the administration of antiandrogens to metastatic male breast cancer patients was proposed. Ever since the use of these compounds has largely been neglected. A therapeutic role for antiandrogens has been envisioned again in recent years. First, molecular characterization efforts pointed to the androgen receptor as a potential therapeutic target. Second, the development of aromatase inhibitors unexpectedly raised the need for neutralizing androgens in order to tackle endocrine feedback mechanisms responsible for acquired resistance. We herein provide an overview of molecular studies where the androgen receptor was investigated at the genomic, transcriptomic or phenotypic level. We then discuss androgens in the context of the endocrine networks nourishing male breast cancer. Finally, clinical evidence on antiandrogens is summarized along with strategies should be implemented to improve the medical management of these patients.

Introduction

Male breast cancer (MBC) is a rare condition [1]. Even though its incidence is raising with peaks in some African countries, MBC accounts approximately for 0.5–1% of all breast cancer (BC) cases [2,3]. Owing to the rarity of the disease, obtaining a clear picture of risk factors is tremendously challenging. MBC is a disease of elderly men, as the incidence increases with age without the bimodal pattern present in female BC (FBC), and develops more commonly in men with underlying medical conditions that lead to a high estrogen/androgen ratio like in the case of Klinefelter's syndrome, testicular disorders, obesity or liver diseases [4,5]. From a genetic perspective, MBC shares some common risk factors with FBC, such as germline mutations in BRCA1and BRCA2 [4]. Additional genetic alterations that have been connected with the onset of MBC involve PALB2, androgen receptor (AR), CYP17, CHEK2, and RAD51B [4].

When considering current therapeutic approaches, it is worth mentioning in advance that the evidence that has been collected so far relate to small-sized, retrospective studies. Attempts to provide prospectively-generated data have indeed been frustrated by the difficulties in enrolling participants. The most established therapeutic concept is that MBC is a tumor largely dependent on sex hormones and the oncogenic activities mediated by their cognate receptors [6]. The therapeutic relevance of hormone manipulations is rooted in surgical procedures, such as orchiectomy, adrenalectomy and hypophysectomy, and dates back to 1940s when orchiectomy was first described as an effective treatment for skeletal metastases [2]. These procedures have largely been replaced by hormonal medical treatments. The impressive progress we have witnessed in the medical treatment of hormone receptor-positive FBC has also had an impact on the management of MBC patients. Two interconnected factors explain this. First, most MBCs are estrogen receptor (ER)-positive, and ER is even expressed at a higher frequency than in FBC [7]. Second, a wave of studies, though retrospective in nature, provided clues that ER-directed therapies are effective for treating MBC patients [8–12]. Antitumor efficacy has been reported with virtually all the antiestrogens currently

Abbreviations: AIs, aromatase inhibitors; AR, androgen receptor; BC, breast cancer; CPA, cyproterone acetate; ER, estrogen receptor; FBC, female breast cancer; FSH, follicle-stimulating hormone; GnRH analogs, gonadotropin-releasing hormone analogs; LH, luteinising hormone; MBC, male.

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available, namely tamoxifen, aromatase inhibitors (AIs) and fulvestrant [8–12].

Even though, one the one hand, antiestrogen therapy has received significant attention over the past decades, on the other hand its increased success has obscured alternative therapeutic strategies. In the mid-1980s Massimo Lopez theorized similarities between MBC and prostate cancer in terms of androgen dependency, and provided seminal evidence that tumor regressions can be achieved with antiandrogens [13,14]. Ever since, the therapeutic potential of antiandrogen therapy remained confined to data extrapolated from a few dozen of metastatic MBC patients. The importance of androgens in MBC was paradoxically proposed again in recent years with the advent of AIs. Patients treated with AIs experience an increase of androgen levels, owing to the drop in 17b-estradiol and the consequent activation of the hypothalamic-pituitary feedback loop. This results in an excess of substrate for aromatization that is supposed to oppose the action of AIs [6].

In this article we discuss molecular and endocrine concepts related to the AR and androgens in MBC. We then illustrate available evidence with antiandrogens in the clinical setting, addressing why AR-directed therapies deserve substantially increased consideration.

AR in MBC: genomics

Large initiatives pursuing global molecular characterization of tumors are shedding light on the molecular landscape of the most common malignancies. Tumors arising in a given body site have been reclassified into a number of molecular subtypes [15]. Once data were accumulated, information gathered from multiple layers of molecular characterization (genomics, transcriptomics, proteomics etc.) were integrated [16]. Nowadays, we have a fairly detailed map of the most commonly deregulated pathways and networks coexisting in a given disease entity. The ultimate goal of this impressive functional characterization is twofold: i) matching specific alterations to drugs that selectively switch off aberrantly activated molecular networks, and ii) avoid wasting resources to develop compounds in tumors that are not reliant on the drug target(s). Given the rarity of MBC, neither the molecular interactions driving the disease nor adaptive changes that enable cancer cells to survive stressful conditions (e.g. pharmacological pressure) have been thoroughly investigated. Since discussing molecular alterations in MBC outside those impacting AR signal is not within this review's scope, for a more comprehensive view on this topic the reader may refer to [17]. Briefly, a first wave of studies with characterization purposes provided preliminary evidence on genetic changes and deregulated pathway nodes that operate in MBC. Although they painted an incomplete picture, AR was the focus of early investigations and its druggability has raised expectations. Although the AR abnormalities/antiandrogen therapy pair is intuitive, the evidence is still scattered and functional preclinical studies are missing.

First evidence that MBCs harbor AR mutations dates back to 1992 when a germline mutation in exon 3, encoding the DNA-binding domain, was reported in two brothers with concomitant clinical and endocrine evidence of androgen resistance (Reifenstein syndrome) [18]. One year later, a point mutation in exon 3 was detected after screening 13 MBC patients for the presence of germline mutations in exons encoding the DNA-binding domain [19]. Again, the patient whose tumor carried this AR mutation presented a partial androgen insensitivity syndrome. Since AR-mutant MBC cases were found in an androgen insensitivity context, a protective role for AR was envisioned. The logic behind this was a mutationally-induced decreased activity of AR that nullifies the protective effects of androgens on the male breast. Conversely, it has also been postulated that mutant AR forms might have altered interactions with partner proteins without defective DNA binding ability [20], or that AR mutants gain an altered sequence-specific DNA binding, enabling them to bind to estrogen response elements (EREs) and then promoting the transcription of estrogen-regulated genes [18,19]. In an endocrine background of elevated estrogen-androgen ratio, like in the case of aged males in whom 17b-estradiol levels are higher than in post-menopausal females [21], this abnormal DNA binding pattern may therefore promote MBC. We cannot rule out alternative possibilities. AR mutations may enhance avidity for androgens, feed promiscuous binding to other ligands, or modify the recruitment and/or balanced activity of co-activators and co-repressors. However, while theories multiplied, the interest surrounding AR mutations was dampened by subsequent case series that failed to provide evidence of germline or somatic mutations [20,22]. A second chapter that further complicates the picture refers to a highly polymorphic region within the coding area of exon 1, containing a variable number of polyglutamine (CAG) repeats. In the general population this region encodes for 17–26 glutamines [23]. An abnormal expansion of this region is seen in patients with X-linked spinal and bulbar muscular atrophy (Kennedy's syndrome), a condition also characterized by androgen insensitivity [23]. Conversely, shorter AR polyglutamine tracts have been associated with increased AR activity in preclinical models, and with an increased risk of prostate cancer [24]. The message conveyed is that shorter CAG tracts translate into an increased AR transcriptional activity, whereas longer CAG tracts result in a suboptimal ligand-mediated stimulation of AR. Two studies searching for an association between CAG repeat length and MBC did not notice any appreciable differences between cases and the respective control groups [22,25]. Two other studies suggested that longer CAG repeats are more common in MBC that in controls [26,27], and a trend toward a higher frequency of shorter CAG tracts in the control group emerged from a fifth report [28]. Thus, even though genetic evidence is scarce and somewhat ambiguous, the scenario proposed is that androgen hyposensitivity caused by either AR mutations or long CAG repeats might be a causal factor for MBC. If AR emanates protective signals in MBC, how is this connected with tumor regression following exposure to antiandrogens? In interpreting genomic studies on AR it is worthwhile looking at the question from a different angle. Genetic alterations in AR seem extremely rare and possibly define tumors arising in specific syndromic contexts or populations. In a small-sized immunohistochemistry-based study analyzing steroid hormone receptor expression hints of lower mean age at diagnosis for AR-negative tumors were provided [29]. This suggests that the molecular relevance of AR might change with aging, and potentially reconnect with the aforementioned studies. Indeed, two of the three AR-mutated tumors were diagnosed in men younger than 60. From a therapeutic perspective, we argue that the ideal setting to investigate the frequency and therapeutic implications of AR mutations, amplifications, or splice-variant expression is not the basal condition, i.e. at diagnosis in therapy-naïve patients, but rather after disease progression following multiple lines of antihormone treatments. As already established in prostate cancer, AR alterations might indeed arise upon prolonged exposure of cancer cells to a hormone-deprived milieu, representing an acquired event that ensures cell fitness in a hostile environment [30].

AR in MBC: transcriptome-based studies

The first attempts of MBC sub-classification have been recently carried out. At the beginning, genomic profiling of MBC revealed the existence of two subgroups defined as male-complex and male-simple [31]. The latter was designated as a disease occurring exclusively in men. The idea of MBC as a heterogeneous disease was further strengthened upon unsupervised hierarchical clustering of gene expression profiling preformed by the same group [32]. With