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EDITORIAL COMMENT

A gender-related dichotomy in bladder cancer

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We read with great interest the research paper entitled "Possible Role of 5-Alpha Reductase Inhibitors in Non-Invasive Bladder Urothelial Neoplasm: Multicentre Study" by Pastore *et al.* published in the current issue of *Minerva Urology and Nephrology*.[1]

The authors analyzed bladder cancer (BC) characteristics and recurrence rates in a cohort of 312 patients with non-muscle invasive BC (NMIBC) which comprised of 165 patients treated with 5-Alpha Reductase Inhibitors (5ARIs) for symptomatic prostatic hyperplasia for a minimum of 12 months prior to transurethral resection of bladder tumor (TURBT) and the control group of 147 untreated patients. Their results demonstrated that patients who received 5ARIs had a significantly greater number of low-grade tumors, a lower rate of recurrences compared to the control arm and a longer recurrence-free survival rate. Their finding supports the hypothesis that:

- androgens and/or androgen receptor (AR) may play a role in bladder cancer carcinogenesis;
- inhibiting or interfering with AR activity may impair bladder cancer progression towards high grade tumors and inhibit cancer invasiveness, thus reducing progression into muscle-invasive BC (MIBC).

This theory is corroborated by epidemiologic data, both *in-vitro* and *in-vivo* studies, and retrospective clinical studies. Males have a substantially higher risk of BC than females. According to GLOBOCAN 2021, the incidence of BC in men is 440.864 *versus* 132.414 cases in women.[2] Gender-specific difference in BC incidence might be explained by differences in carcinogens exposure, such as smoking and occupational risk factors, although it is plausible that androgen exposure may also play a role. Although BC has always been thought to be a hormone-independent tumor, AR expression has been detected in histopathological specimens of normal and neoplastic urothelium in both male and female patients. AR expression was identified in 75% of superficial (Ta and CIS) lesions and in 21% of MIBC.[3]

This dichotomy in the incidence of BC between sexes has been investigated by a preclinical study on mice by Miyamoto *et al.*[4] Indeed,

when male and female mice were exposed to N -butyl- N -(4- hydroxybutyl) nitrosamine, a well-established BC carcinogen, 92% of males *versus* 42% of females developed urothelial cancer. When the same experiment was performed using AR knockout mice in males and females, none of them developed BC. Further, the treatment of human BC cells expressing AR and xenograft tumor with androgen inhibitors or Flutamide successfully inhibited cell proliferation and growth. These experiments demonstrated the chemopreventive and the therapeutic effect of inhibiting AR signaling pathways in cellular and mouse models.[4]

A more recent hypothesis to explain the higher incidence of BC in males suggest that the ability of testosterone to mediate the exhaustion of T cells in the tumor microenvironment through an AR- independent mechanism may play a role, while females may be protected by elevated circulating estrogens which may act as an immune activator.[5]

These differences in gender specific-features of BC have also been evidenced by the new molecular classification of MIBC. The basal/squamous subtype of BC is significantly more frequent in females compared to males, and is associated with a more aggressive phenotype.[6] This molecular classification is in line with the dual track carcinogenesis concept, according to which BC may arise via two distinct pathways, papillary and non-papillary.[7] More than 80% of urothelial tumors arise from non-muscle invasive disease that may recur, with the minority of cases progressing to MIBC. The remaining 20% develop from the non-papillary pathway and typically presents as solid, invasive tumors, often preceded by carcinoma *in situ*. These non-papillary tumors have a different genomic signature, and in most cases are of the basal/squamous phenotype, which may benefit from a different treatment strategy.[8]

The results from the analysis of regulon status of different genes and pathways in MIBC RNA-sequencing data included in the consensus study also support this hypothesis.[6] Indeed, the regulon of AR demonstrated to be active in the luminal subtypes of BC and completely inactive in the basal/squamous subtype.[6] Several findings suggest that BC may initially be an AR dependent disease but may progressively lose this dependency in higher T-stage. Multiple retrospective studies have reported the benefit in overall and cancer-specific survival in patients who receive 5-ARIs and androgen-deprivation therapy (ADT). However, their protective effect seems more evident in low-risk disease compared to patients with high-risk disease.[9] This is consistent with immunohistochemical studies where AR expression is more frequently over expressed in low- grade BC.[3]

However, most published studies utilizing retrospective datasets included a very low number of patients treated with potent androgen inhibitors or AR antagonists, which according to *in-vitro* studies and mouse models, have a greater therapeutic efficacy. Prospective clinical studies are needed to investigate the role of androgens in BC. To date, only one trial (NCT02605863) has attempted to explore the therapeutic role of enzalutamide in the prevention of NMIBC recurrences. Unfortunately, due to low enrollment and sponsor withdrawal, the study was terminated in 2018. Further dissection of detailed mechanisms of initiation and progression of bladder cancer will be fundamental to find other therapeutic targets both in the initial and in the advanced stage targeting either androgens and/or the AR signaling might be the next step toward this goal and merit consideration for clinical testing.

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