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Enhancing Sex Based Reactions to Bladder Cancer Treatment

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Introduction

In the USA, there will likely be 81,000 new cases of Bladder Cancer (BCa) in 2022, with men having nearly three times as many cases as women. Despite having a lower incidence, women usually have had more severe cancers and worse oncological outcomes, including higher rates of cancer specific mortality, disease progression and recurrence. As demonstrated by the standard of care condition of Bacillus Calmette-Guerin (BCG) immunotherapy in Non-Muscle Invasive BCa (NMIBC) and the recent approval of Immune Checkpoint Inhibitor (ICI) therapies targeting the PD-1/PD-L1 axis in NMIBC, modulating a patient's immune system is a genuine therapeutic option for BCa. Recurrences can be common despite improvements in immune based therapy and we lack reliable predictive indicators of treatment response [1].

Description

Men and women reacted differently to systemic immunotherapy, demonstrating sex specific differences in immune physiology and responses to pathogenic insults. Therefore, research that give insight on sex's significance as a "biomarker" of immunomodulatory therapy response may be used to enhance risk stratification, boost response rates and discover brand new therapeutic targets [2]. Besançon elegantly assessed the influence of sex on the androgen mediated response to immunotherapy in a previous edition of European urology open science. To demonstrate that mouse biology at least approximates the sex specific makeup and differences in human immune physiology, the authors first validated there *in vivo* NMIBC model using comparable patient tissue samples.

Then, they found utilizing their model that enzalutamide, an antagonist of an Androgen Receptor (AR), combined with either local BCG immunotherapy or systemic anti-PD-1 immunotherapy, improved tumour control and survival in male mice. Enzalutamide has a minor potentiating effect on the prevention of tumour development, but it has a very noticeable potentiating effect on survival curves, which is a promising preclinical finding [3]. It's interesting to note that the scientists' research on male mice revealed that therapy with enzalutamide alone increased tumour growth and decreased survival. Although the tumour development and survival curves for the female mice using enzalutamide alone are not provided for comparison, this result lends support to the idea that AR signalling may play a role in the sex specific variations in BCa.

Men are more likely than women to suffer BCa, even after trying to take smoking, exposure to the environment and workplace hazards into account. This differential in incidence may be caused by sex specific variations in AR signalling. Through a series of flow cytometry and RNA sequencing experiments, the authors hypothesized that enzalutamide mechanistically modifies the ratio of lymphocytes that infiltrate tumours to produce a tumour micro-environment that cooperates with both ICIs and BCG. The authors demonstrate that this may also be true for BCa models. It has also been hypothesized that AR signalling has an immunosuppressive effect in the context of prostate cancer models [4].

Novel anti-androgens' immunomodulatory features point to a justifiable application in BCa as an adjuvant to immunotherapeutic drugs rather than a monotherapy. Particularly instructive in this regard is the authors' finding for enzalutamide alone in the current investigation. Indeed, enzalutamide and the ICI pembrolizumab have showed promising benefits in on-going trials for metastatic prostate cancer.

Examining the effects of AR antagonism in MIBC would be a logical progression from the current research because the potential for enhancing treatment responses in males could be larger in this situation. We have demonstrated that MIBC demonstrates sex bias at the molecular level, beyond the epidemiological level, with males more likely to have luminal papillary tumours and tumours with higher androgen response activity across the board throughout every luminal subtype. Additionally, the luminal papillary MIBC subtype is more prevalent in AR. In preclinical models of MIBC, it has been demonstrated that AR antagonism is synergistic with cisplatin based chemotherapy. It is anticipated that AR antagonism would exhibit a similar synergy with new ICIs in MIBC. Based on the high level of AR expression and signalling activity in this particular cohort, we expect that males with luminal papillary tumours would benefit most from the treatment [5].

Despite the limited sample sizes for the treatment groups, the authors' preclinical findings offer a solid foundation for clinical studies to assess the approach of combining anti-androgen therapy with current immunotherapies in NMIBC to increase treatment response rates, at least in men.

Conclusion

We commend the authors for demonstrating that anti-androgens can enhance immunotherapy response in males with NMIBC, but we urge researchers to look into similar approaches to improve treatment results in MIBC and, more crucially, in women. As things stand, immunotherapy treatment outcomes seem to favour males over women, most likely as a result of the interaction between innately sex specific immunobiology and gender as a social determinant of health. Perhaps the apparent baseline treatment advantage that the female mice in the current study experienced is a reflection of what might have been in the absence of health care inequities, delayed diagnosis and access to treatment hurdles, among other things.

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