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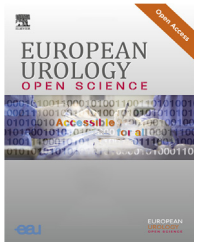

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Opinion: Open Science

Sex-specific Augmentation of Treatment Responses in Bladder Cancer

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An estimated 81 000 new cases of bladder cancer (BCa) will be diagnosed in the USA in 2022, with three times as many cases among men as among women [1]. Despite lower incidence, women tend to have more aggressive disease and worse oncological outcomes, including higher rates of disease recurrence, progression, and cancer-specific mortality [2]. Modulating a patient's immune system is a bona fide strategy for treating BCa, as evidenced by bacillus Calmette-Guérin (BCG) immunotherapy being standard of care 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. Despite advances in immune-based therapies, recurrences can be frequent and we lack robust predictive biomarkers of treatment response. Results from systemic immunotherapy trials have shown differential responses in females and males, highlighting sex-specific variations in immune physiology and responses to pathogenic insults. Thus, studies that elucidate a deeper understanding of sex as a "biomarker" of response to immunomodulatory therapies may be leveraged to improve risk stratification and response rates and identify new therapeutic targets.

In a previous issue of *European Urology Open Science*, Besançon et al. [3] elegantly examined the effect of sex on androgen-mediated response to immunotherapy. The authors first validated their in vivo NMIBC model with corresponding patient tissue samples to show that mouse biology at least recapitulates the sex-specific composition and variations in human immune physiology. They used their model to then show that combining the androgen receptor (AR) antagonist enzalutamide with either local BCG immunotherapy or systemic anti-PD-1 immunotherapy provided enhanced tumor control and survival among male mice. While the potentiating effect of enzalutamide on tumor growth inhibition is somewhat modest, the potentiating effect on the survival curves is quite striking and represents a promising preclinical result. Interestingly, the authors showed that treatment with enzalutamide alone resulted in tumor growth and worse survival among male mice. Although the tumor growth and survival curves are not shown for enzalutamide alone for the female mice for comparison, this result supports the putative role of AR signaling in sex-specific differences in BCa. As mentioned, men are at higher risk of developing BCa in comparison to women, even after accounting for smoking and environmental and occupational exposures. Sex-specific differences in AR signaling could be one factor driving this disparity in incidence.

The authors performed a series of flow cytometry and RNA-sequencing studies to suggest that, mechanistically, enzalutamide alters the balance of tumor-infiltrating lymphocytes to create a tumor microenvironment that synergizes with both ICIs and BCG. It has also been postulated that AR signaling has an immunosuppressive effect in the setting of prostate cancer models [4], which the authors show might also be the case in BCa models. The immunomodulatory properties of novel antiandrogen agents (abiraterone, enzalutamide) suggest a rational use case as an adjunct to immunotherapeutic agents rather than monotherapy in BCa. The authors' result for enzalutamide alone in the current study is particularly telling in this regard. Indeed, ongoing trials combining enzalutamide and the ICI pembrolizumab in metastatic prostate cancer have shown promising results.

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A logical next step from the current work would be to evaluate the effects of AR antagonism in MIBC, as the potential for augmenting treatment responses in males could be on a greater scale in this setting. Beyond the epidemiological level, we have shown that MIBC exhibits sex bias at the molecular level, with males more likely to have luminal papillary tumors and tumors with higher androgen response activity across all luminal subtypes [5]. Moreover, AR is enriched in the luminal papillary subtype of MIBC [6]. It has been shown that AR antagonism is synergistic with cisplatin-based chemotherapy in preclinical models of MIBC [6] and it is likely that AR antagonism would exhibit similar synergy with novel ICIs in MIBC. We hypothesize that the greatest benefit would be seen for males with luminal papillary tumors on the basis of the high degree of AR expression and signaling activity in this specific population.

Notwithstanding the small sample sizes for the treatment groups, the preclinical results reported by the authors are a promising basis for clinical trials to evaluate the strategy of combining antiandrogen therapy with current immunotherapies in NMIBC to augment treatment response rates, at least in men. But what about women? Interestingly, the authors' murine model of NMIBC had a baseline deficit in survival and response rates to either BCG or anti-PD-1 alone for male compared to female mice (which was rescued with enzalutamide). Clinically, we observe conflicting findings: women with BCa are less sensitive to and experience worse outcomes with local and novel systemic immunotherapies [7,8]. Although this may be attributed to external variables (social determinants of health, medications such as antibiotic use, among other factors), there is a greater need to develop effective strategies to augment the therapeutic response in women. The anti-estrogen tamoxifen could represent a viable sensitization strategy given that preclinical studies have shown its ability to enhance the effect of BCG [9] and the ability of estrogen receptor activation to downregulate sensitivity to anti-PD-1 immunotherapies in breast cancer [10]. Results from a phase 2 trial evaluating tamoxifen monotherapy in NMIBC (NCT02197897) are currently pending, and perhaps further avenues of research could investigate combining tamoxifen with immunotherapies in both NMIBC—ideally with high-fidelity preclinical models such as the one used by the authors—and MIBC, taking into account molecular subtypes, for a potential sex-biased treatment response in favor of females.

In conclusion, we applaud the authors for showing the potential of antiandrogens to augment response to immunotherapy in men with NMIBC, but we call for investigators to examine similar strategies to improve treatment outcomes in MIBC and, more importantly, in women. As it currently stands, treatment outcomes with immunotherapy appear to be sex-biased against women, probably resulting from an interplay between inherent sex-specific immunobiology and gender as a social determinant of health. Perhaps the apparent baseline treatment advantage experienced by the female mice in the current study reflects what could be in the absence of delays in diagnosis, barriers in access to treatment, and health care disparities, among other factors.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7–33. https://doi.org/10.3322/caac.21708.
[2] Scosyrev E, Noyes K, Feng C, Messing E. Sex and racial differences in bladder cancer presentation and mortality in the US. Cancer 2009;115:68–74. https://doi.org/10.1002/cncr.23986.
[3] Besançon M, Gris T, Joncas F-H, et al. Combining antiandrogens with immunotherapy for bladder cancer treatment. Eur Urol Open Sci 2022;43:35–44. https://doi.org/10.1016/j.euros.2022.06.007.
[4] Ardiani A, Gameiro SR, Kwilas AR, Donahue RN, Hodge JW. Androgen deprivation therapy sensitizes prostate cancer cells to T-cell killing through androgen receptor dependent modulation of the apoptotic pathway. Oncotarget 2014;5:9335–48. https://doi.org/10.18632/oncotarget.2429.
[5] de Jong JJ, Boormans JL, van Rhijn BWG, et al. Distribution of molecular subtypes in muscle-invasive bladder cancer is driven by sex-specific differences. Eur Urol Oncol 2020;3:420–3. https://doi.org/10.1016/j.euo.2020.02.010.
[6] Tripathi A, Gupta S. Androgen receptor in bladder cancer: a promising therapeutic target. Asian J Urol 2020;7:284–90. https://doi.org/10.1016/j.ajur.2020.05.011.
[7] Uhlig A, Strauss A, Seif Amir Hosseini A, et al. Gender-specific differences in recurrence of non-muscle-invasive bladder cancer: a systematic review and meta-analysis. Eur Urol Focus 2018;4:924–36. https://doi.org/10.1016/j.euf.2017.08.007.
[8] Wang P-F, Song H-F, Zhang Q, Yan C-X. Pan-cancer immunogenomic analyses reveal sex disparity in the efficacy of cancer immunotherapy. Eur J Cancer 2020;126:136–8. https://doi.org/10.1016/j.ejca.2019.12.008.
[9] Shang Z, Li Y, Hsu I, et al. Targeting estrogen/estrogen receptor alpha enhances bacillus Calmette-Guérin efficacy in bladder cancer. Oncotarget 2016;7:27325–35. https://doi.org/10.18632/oncotarget.8756.
[10] Goto T, Miyamoto H. The role of estrogen receptors in urothelial cancer. Front Endocrinol 2021;12:643870. https://doi.org/10.3389/fendo.2021.643870.