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European Association of Urology

Letter to the Editor

Re: Russell Szmulewitz, Supriya Mohile, Edwin Posadas, et al. A Randomized Phase 1 Study of Testosterone Replacement for Patients with Low-Risk Castration-Resistant Prosate Cancer Eur Urol 2009; 56:97–104

Szmulewitz et al. [1] treated low-risk castration-resistant prostate cancer (PCa) patients with testosterone (T) without doing anything to prevent the conversion of T to estradiol (E2) by aromatase. In referring to this study, van der Poel [2] correctly pointed out that "it is far from clear whether these increased estrogen levels are, by definition, beneficial." Ordinarily, there is no aromatase activity in normal prostate epithelial cells, but there is in PCa [3]. Therefore, an increase in T would be expected to cause a greater increase in the local E2 level around the PCa than in the serum E2 level. Because estrogen receptor-α (ER-α) promotes PCa growth and ER-β promotes PCa death [4], in the short time frame of the study, the effects of E2 on the ERs may mask the effect of T on the androgen receptors (ARs). E2 can be either beneficial or harmful, depending on the initial levels of the various ERs. In the long run, the expected outcome is much more clear cut.

Eventually, those PCa cells with higher levels of ER-α and lower levels of ER-β will have a selective growth advantage over cells with more normal levels of the ERs. Natural selection would be expected to alter the phenotype of the PCa population to move in this direction, and in fact, ER-α activity tends to increase as PCa progresses, with the highest levels observed in metastatic PCa and in hormone-refractory PCa [4]. By the laws of natural selection, higher levels of E2 would be expected to hasten this process. Therefore, it is clear that allowing T to be converted to E2 will always be harmful. One obvious solution would be to use an antagonist to ER-α. Although ER-α upregulates the strongly antiapoptotic protein B-cell leukemia/lymphoma 2 (Bcl-2) and ER-β downregulates Bcl-2, membrane ER (mER) may well upregulate Bcl-2 [5]. Until safe and effective antagonists to both ER-α and mER are developed, aromatase inhibitors are the only way to avoid long-term harm to PCa patients as a result of T being converted to E2. In the short term, it may be helpful to some patients not to receive aromatase inhibitors, but it makes no sense to withhold aromatase inhibitors once there is any evidence of disease progression.

Another advantage of using aromatase inhibitors is that it allows the studies involving T and PCa to isolate the action of T on ARs separate from the action of E2 on ERs. Because all of the classical studies in the past that administered T to men with PCa never used aromatase inhibitors, there is no way to tell to what extent the observed results were due to the effect of T on the ARs and to what extent they were due to the effect of E2 on the ERs.

Conflicts of interest: The author has nothing to disclose.

References

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