Targeting the Androgen Receptor Signaling Axis to Reduce Testosterone Levels in Prostate Cancer: How Low Should We Go?

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Source:

Almost three-quarters of a century have elapsed since the Nobel Prize–winning discovery by Huggins and Hodges of the androgen dependence of prostate cancer, and blockade of the androgen receptor (AR)-signaling pathway remains a cornerstone of treatment.[1] As reviewed by Dr. Bastos and his colleagues in this issue of ONCOLOGY, it is now well established that castration-resistant disease can be effectively treated using newer AR-targeting agents such as abiraterone and enzalutamide.[2]

Blockade of AR signaling via inhibition of testosterone synthesis or by AR antagonism is not a novel concept, given that first-generation anti-androgen therapy employed ketoconazole (a CYP17 inhibitor like abiraterone) and bicalutamide, nilutamide, and flutamide (anti-androgens like enzalutamide). The newer agents have the advantage of increased potency relative to the first-generation agents, while maintaining relatively low toxicity, particularly compared to docetaxel. As discussed by Bastos et al, the phase III clinical trials in the pre- and post-docetaxel settings have demonstrated impressive clinical benefit using AR-targeting therapy. These results have led to US Food and Drug Administration approval of abiraterone and enzalutamide, as well as development of other oral hormonal agents in clinical trials, such as the anti-androgens ARN-509[3] and ODM-201, the CYP17 inhibitor orteronel (formerly TAK-700), and the combination anti-androgen and CYP17 inhibitor galeterone (refer to clinicaltrials.gov for specifics).

We agree with Bastos and colleagues that one of the most pressing research needs is a better understanding of the spectrum and overlap of the different AR-targeting drugs, and of mechanisms of resistance to these agents. Emerging clinical data suggest a substantial but not complete overlap in mechanisms of resistance to abiraterone and enzalutamide, including upregulation of steroidogenic enzymes like CYP17,[4] emergence of AR splice variants,[5,6] and alternative pathways such as via phosphatidylinositol 3 kinase (PI3K)/mammalian target of rapamycin (mTOR) or the glucocorticoid receptor.[7,8] Of note, there are two Stand Up to Cancer/Prostate Cancer Foundation–funded efforts to molecularly characterize biopsied metastases from patients resistant to abiraterone and enzalutamide (see www.standup2cancer.org). The results of these investigations are eagerly anticipated.

In the meantime, work is ongoing to apply what we have already learned to help develop predictive biomarkers for the treatment of metastatic castration-resistant prostate cancer (mCRPC). At the 2014 meeting of the American Society of Clinical Oncology (ASCO), for example, Antonarakis et al reported their findings of detection of the AR splice variant-7 (AR-V7) in the blood (from circulating tumor cells) of patients treated with abiraterone and enzalutamide.[1] The presence of AR-V7 correlated with lack of response to abiraterone and enzalutamide, suggesting that, if validated, this strategy could be applied to help guide treatment involving AR-targeted agents. Additional strategies include development of drugs targeting the less dispensable N-terminal domain of AR, for example, small-molecule sintokamide peptides and the AR N-terminal domain decoy EPI-001.[9,10]

With the growing body of data indicating that cross-resistance between AR-targeted agents will remain a formidable problem, at least in the near term, we wonder how much ground can be gained by either switching to, or combining with, agents that function via a different mechanism of action. The recent impressive results of the CHAARTED study (ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) suggest that in the appropriate scenario, combination chemotherapy with hormonal therapy is more effective,[11] leading us to ponder whether this could also be an effective strategy in the setting of mCRPC. One could imagine that combining an AR-targeting agent with taxanes, radium-223, and/or sipuleucel-T could be additive or possibly synergistic; studies addressing some combinations of these agents are underway
or in development (see clinicaltrials.gov).

Although the bulk of collective effort has been aimed at annihilating the androgen axis, there is also an emerging appreciation for the bifunctional role of steroid hormones.[12] Preclinical studies suggest that testosterone boost results in downregulation not only of AR but also AR-V7 in a castration-resistant cell line. Thus, there may be an appropriate time to reintroduce androgens rather than continue to eradicate every molecule of testosterone and dihydrotestosterone.[13] Indeed, a pilot study of rapid cycling between supraphysiologic and castrate levels of testosterone in men with CRPC demonstrated preliminary efficacy as measured by prostate-specific antigen, and objective responses were reported at ASCO 2014 by Schweizer et al.[14] We are intrigued by this inventive approach and look forward to seeing more results from this line of strategy.

While we share the enthusiasm for the plethora of new AR-targeting agents, we also question the degree to which ever-deeper suppression of the androgen axis will facilitate emergence of AR-independent tumors (eg, those with neuroendocrine, anaplastic, and small-cell histologies).[15-17] In light of growing evidence to support this effect, there is a real need to develop new therapies for these patients with true androgen/AR-independent disease.[17,18]

As we explore use of these agents in earlier disease settings, men may be faced with a longer duration of treatment, potentially compounding the toxicities that were previously more acceptable in patients treated during the later stages of disease. In addition, the likelihood of developing resistance is increased with longer duration of treatment with an oral agent, a setting in which compliance may become less reliable. (Consider experiences in treating chronic myelogenous leukemia and human immunodeficiency virus I where resistance emerges as compliance wanes.) There is no question that these are exciting times for management of prostate cancer, since we have a wealth of new agents available, many of which target the AR. The challenge for investigators and clinicians is in how to maximize benefit and minimize toxicities, and for patients we cannot cure, to continue pushing the envelope to maximize their length and quality of life.

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