Targeting the Androgen Receptor: Past, Present and Future

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The Importance of the Androgen Receptor in Castrate-Resistant Prostate Cancer

The androgen receptor (AR) is expressed in the non-castrate state of prostate cancer, but as patients progress through the non-castrate state into castration-resistant disease, the AR is overexpressed and sensitizes tumors to low levels of androgen. When the AR is overexpressed in the castration-resistant state, some of the mechanisms that lead to resistance are involved with agonist activity. In this way, AR can actually mutate and become promiscuous, binding to other ligands. When the AR binds to ligands, it moves into the cell’s nucleus and initiates transcription of AR target genes that are involved in cell growth and survival. Androgen antagonists, such as bicalutamide, are weak and reversible inhibitors. Bicalutamide, therefore, can actually convert from an antagonist into an agonist, resulting in stimulation, rather than control of the disease [1,2].

Androgen-Receptor Targeted Therapies Offer Benefits for Castrate-Resistant Prostate Cancer

The androgen receptor has been the focus of intense clinical research over the past few years. While multiple AR signaling targets have been identified, to date the most successful have been inhibition of adrenal and intratumoral synthesis of androgens (abiraterone) and AR antagonism that impairs translocation of the androgen receptor into the nucleus (enzalutamide).

Abiraterone

Abiraterone acetate inhibits the CYP17 family. Inhibition of C17-20-lyase downregulates androgen precursors and, ultimately, the potent ligand dihydrotestosterone. It also inhibits 17α-hydroxylase, which results in downregulation of cortisol. When the brain senses the low cortisol levels, it upregulates, ACTH, which can cause a secondary mineral cortical syndrome with fluid retention, hypertension, and hypokalemia. To mitigate this potential toxicity, most of the trials using abiraterone today use a low dose of glucocorticoid, typically prednisone [3].

A 2011 landmark abiraterone study in patients with metastatic castrate resistant prostate cancer showed that the AR is an important therapeutic target in castrate-resistant prostate cancer [4]. Based on these results in metastatic castration-resistant prostate cancer after chemotherapy and the very favorable toxicity profile, Study 302 looked at abiraterone earlier in the disease state for patients with metastatic castration-resistant prostate cancers who were minimally symptomatic or asymptomatic and had not yet received chemotherapy [5]. Abiraterone doubled the time to radiographic progression-free survival (median, 16.5 months for abiraterone; 8.3 months for prednisone) and favored survival, but did not cross the prespecified significance value, which was a p value of .0035 [6]. With respect to secondary endpoints for this trial, abiraterone was associated with significantly longer time to opiate use for cancer-related pain, time to chemotherapy initiation, time to deterioration of performance status, and time to PSA progression [6].

Enzalutamide

In its unbound state in the cytoplasm, the AR is bound to HSP90. When it binds to ligand, it undergoes a transformational change, and this transformational complex then translocates into the nucleus. Enzalutamide is a second-generation AR antagonist (previously known as MDV3100) that impairs nuclear import, DNA binding, and coactivator recruitment [7].

The AFFIRM trial evaluated the efficacy and safety of enzalutamide in post-chemotherapy metastatic castration-resistant prostate cancer patients; treatment with enzalutamide was associated with a 30%–37% reduction in the risk of death. Fatigue was the most common adverse event associated with enzalutamide [8]. The incidence of seizure in the AFFIRM study was very low—0.6%. Patients who experienced a seizure in this study either had brain metastases or were on drugs that could lower the seizure threshold [9].
ARN-509, a Novel AR Antagonist

The phase I/II study looked at the novel second generation AR antagonist ARN-509 in patients with progressive castration-resistant prostate cancer patients [10]. The PSA response rate was 80%–90% in patients with castration-resistant prostate cancer, with or without metastatic disease [11,12]. In patients previously treated with at least 6 months of abiraterone, 24% met the PSA response of ≥50% decline at 12 weeks; however, PSA declined to some degree in approximately 50% [12].

Resistance to AR-Targeted Therapies

Biologic predictors of sensitivity and resistance to AR targeted therapies may be similar, regardless of the mechanism of action of the drug. In looking at patterns of PSA and radiographic progression-free survival response in patients treated with abiraterone and enzalutamide, there appear to be three different patient groups. The first are responders to enzalutamide, who have a very rapid and durable decline in PSA but may acquire resistance over time. The second group does not respond at all to abiraterone; they most likely have primary resistance to this type of therapy. The third is an intermediate group that has an initial decline from baseline in PSA, but over time the PSA begins to drift. These patients probably have a different mechanism of response and resistance to these kinds of drugs [13].

Prostate cancer is a heterogeneous disease and biomarkers to individualize therapy will be critical to the future of therapy for patients in need. The challenge moving forward is to better understand what drives different types of responses in order to individualize treatment and optimize outcomes.

References