Sequence and Cross-Resistance: Challenges for Optimal Use of Next-Generation Anti-Androgen Therapies

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Abstract

Use of "next-generation" hormonal therapy for metastatic castration-resistant prostate cancer following the FDA approvals of abiraterone and enzalutamide has allowed for some early observations: 20% to 30% of patients are unresponsive to both of these agents up front; 20% to 30% have transient responses of 2 to 3 months; and the remainder have significant benefit, with a small subset having long-term response. A high degree of cross-resistance between abiraterone and enzalutamide has also been observed, limiting routine sequential use of these well-tolerated drugs.

Key words: anti-androgens, metastatic castration-resistant prostate cancer, enzalutamide, abiraterone

Our entry into "next-generation" hormonal therapy for metastatic castration-resistant prostate cancer (mCRPC) following the FDA approvals of abiraterone and enzalutamide has matured enough for some important, albeit early, observations: 20% to 30% of patients are unresponsive to both of these agents up front; 20% to 30% have transient responses of 2 to 3 months; and the remainder have significant benefit, with a small subset having long-term response.[1] Additionally, we have observed a high degree of cross-resistance between abiraterone and enzalutamide, dashing our hopes for the routine sequential use of these well-tolerated drugs.

Mechanisms of Resistance to Androgen Receptor–Directed Therapies

The androgen receptor remains a key target in mCRPC, and many investigative groups are pursuing hypotheses to explain de novo and acquired resistance.

Treatment of advanced prostate cancer with gonadal testosterone-deprivation therapy using either medical or surgical castration eventually leads to the development of CRPC, which evolves due to tumors developing the capability of synthesizing their own testosterone and/or dihydrotestosterone from precursors, as well as other mechanisms of stimulating the androgen receptor (AR).[2,3] Ferraldeschi and colleagues[3] have identified a gain-of-stability mutation that leads to a gain of function in 3βHSD1, an enzyme that catalyzes the initial rate-limiting step in converting the adrenal-derived dehydroepiandrosterone to the most potent androgen, dihydrotestosterone. The population frequency of this is approximately 22% but appears to vary widely by ethnicity. Work is ongoing to develop a competitive small-molecule inhibitor of 3βHSD1, and a sensitive and specific molecular assay for detection of *3βHSD1* mutations.[4]

Androgen receptor splice variants encode for truncated AR proteins that cannot bind to the ligand, but retain activity as transcription factors that are capable of promoting activation of target genes. Antonarakis and colleagues[5] prospectively evaluated the AR splice variant 7 (AR-V7) in circulating tumor cells from patients receiving enzalutamide or abiraterone, with the goal of predicting response or resistance to these agents. Endpoints of their evaluation included PSA response, clinical or radiographic progression, and both progression-free survival (PFS) and overall survival (OS).

A total of 62 patients (31 patients for each therapy) received enzalutamide or abiraterone, of whom 39% and 19%, respectively, had detectable AR-V7 in circulating tumor cells. Men whose tumors were AR-V7-positive had lower PSA response and time to PSA progression, as well as shorter clinical or radiographic PFS following treatment with either abiraterone or enzalutamide. For patients in both groups, OS was shorter in men with detectable AR-V7 at baseline than among those with undetectable AR-V7. Of note, no AR-V7-positive patient had any meaningful clinical benefit from enzalutamide or abiraterone therapy.[5]

Yet another recently defined potential resistance pathway, reported by Arora and colleagues,[6] involves an increased expression of the glucocorticoid receptor that has potential to explain the development of resistance to enzalutamide in subsets of patients.

Clinical Implications of Resistance

The initial enthusiasm generated by approvals of the next-generation AR-targeted agents abiraterone and enzalutamide has been

tempered somewhat by the limited efficacy when these agents are used sequentially.

Schrader et al[7] recently reported on 35 patients with mCRPC treated with enzalutamide following therapy with abiraterone/prednisone and docetaxel. In this group, the median duration of prior abiraterone treatment was 9 months (range, 2-19 mo), with 16 patients demonstrating a greater than 50% decline in PSA as their best response. The median duration of subsequent enzalutamide therapy was 4.9 months. Seven of 16 patients (44%) who were initially abiraterone-sensitive and 3 of 19 patients (16%) who were initially abiraterone-insensitive experienced a greater than 50% PSA decline while taking enzalutamide.[7]

Noonan and colleagues[8] recently reported on 30 patients from a number of centers treated with enzalutamide in the phase III AFFIRM study who were subsequently managed with abiraterone/prednisone. Of 27 evaluable patients, the median enzalutamide treatment duration was 41 weeks (range, 6-95 wk). Subsequent abiraterone/prednisone treatment duration was 13 weeks (range, 1-52 wk). No objective radiographic responses were observed, and the median abiraterone time to progression was 15.4 weeks, with a median OS of 50.1 weeks.

Loriot et al[9] reported on 38 patients who had evidence of progressive disease following therapy with docetaxel and enzalutamide subsequently treated with abiraterone/prednisone. Only 3 patients (8%) attained a 50% or greater PSA response, with a median PFS of only 2.7 months.

The mounting evidence of cross-resistance of abiraterone/prednisone with enzalutamide has a number of important clinical implications. In patients managed with either abiraterone/prednisone or enzalutamide as initial therapy, the selection of therapy at time of disease progression may require a more nuanced decision process. In patients who are asymptomatic or minimally symptomatic, crossover to the alternative agent may be reasonable, as the cross-resistance observed is not absolute, and some patients may in fact benefit from this approach, given the tolerability of these agents. In patients with symptomatic disease progression, in the opinion of the author, it may be preferable to select what appear to be more active agents, such as docetaxel, or in patients with bone-only disease, radium-223.

Several ongoing clinical trials hopefully will inform some of the many ongoing management questions. The US Intergroup study A031201 will randomize more than 1200 men with mCRPC to receive enzalutamide or the combination of enzalutamide plus abiraterone/prednisone. This trial will address the issue of concomitant targeting of different AR pathways, as well as allow analysis of subsequent AR-directed therapies in patients randomized to enzalutamide alone. The PRIMCAB study (NCT02379390) is a randomized phase II trial that will enroll patients with mCRPC who have progressed on either abiraterone/prednisone or enzalutamide to receive cabazitaxel 25 mg/m^2 versus the alternative AR inhibitor. This will provide prospective data regarding cross-resistance to the alternative AR agent, as well as some clinical evidence regarding the relative utility of chemotherapy in that setting.

Over the next several years, we can look to the potential development of predictive biomarkers to inform clinicians regarding optimal drug selection, in combination with prospective data generated from randomized trials to better enable optimal management of patients with mCRPC.

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Disclosure: Dr Dreicer is a member of a Data and Safety Monitoring Board for Medivation.
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