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: 15% to 25% 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 median responses in the 9- to 15-month range. 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 still early, observations: 15% to 25% 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 median responses in the 9- to 15-month range. A high degree of cross-resistance between abiraterone and enzalutamide has also been observed, limiting 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 medical or surgical castration eventually leads to the development of CRPC, which evolves in part as a consequence of the ability of prostate cells developing the capability of synthesizing its own testosterone and/or dihydrotestosterone from precursors, as well as other mechanisms of stimulating the androgen receptor (AR). Silberstein and colleagues have divided these resistance mechanisms into three broad groups: persistent androgen/AR-signaling, AR bypass pathways and androgen/AR-independent mechanism. Ferraldeschi and colleagues have identified a gain-of-stability mutation that leads to a gain of function in 3ßHSD1, 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. Efforts are ongoing to develop a competitive small-molecule inhibitor of 3ßHSD1, and a sensitive and specific molecular assay for detection of 3ßHSD1 mutations.

Other proposed mechanisms of resistance include glucocorticoid activation of the AR, and the presence of non-AR splice variant other AR mutations.
Clinical Implications of Resistance

The initial enthusiasm generated by approvals of the next-gener- ation AR-targeted agents abiraterone and enzalutamide has been tempered somewhat by the limited efficacy when these agents are used sequentially.

Nadal et al8 reported on 126 patients with mCRPC treated following progression with either enzalutamide or abiraterone with the alternative agent. The majority of patients received enzalutamide (87%) in this setting. PSA-responses were seen in only 22.4% of patients with a median progression free survival of 3.6 months.

Schrader et al9 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 months), with 16 patients demonstrating a greater than 50% decline in PSA as their best response. The median duration of subsequent enzalut- amide therapy was 4.9 months. Seven of 16 patients (44%) who were initially abiraterone-sensitive and 3 of 19 pa- patients (16%) who were initially abiraterone-insensitive experienced a greater than 50% PSA decline while taking enzalutamide.7

Noonan and colleagues10 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 weeks). Subsequent abiraterone/prednisone treatment duration was 13 weeks (range, 1-52 weeks). 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.

The mounting evidence of cross-resistance of abi- raterone/ prednisone with enzalutamide has a number of important clin- ical implications. In patients managed with either abiraterone/ prednisone or enzalutamide as initial therapy, the selection of therapy at time-of-disease progres- sion may require a more nu- anced decision process. In patients who are asymptomatic or minimally symptomat- ic, 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 (NCT01949337) has re- cently completed enrollment of more than 1200 men with mCRPC who were randomized to receive enzalutamide or the combination of en- zalutamide plus abiraterone/predn- isone. This trial will address the issue of concomitant target- ing of different AR pathways, as well as allow analysis of subsequent AR-directed therapies in pa- tients randomized to enzalutamide alone.

Another important study is a randomized phase 2 study led by investigators of the BC Cancer Agency in Canada, where patients are randomly assigned to abiraterone or enzalutamide and then switched to the alternative agent at time of disease progression. This trial will provide pro- spective evidence of the true rate of resistance and has a number of potentially informative correlative studies embedded in the trial (NCT02125357).

A number of novel agents with the potential to overcome the resistance seen with abiraterone and enzalutamide are currently under evaluation. Although a randomized trial of the novel agent galeterone was stopped early for lack of efficacy, other agents such as a VT-464, a lyase-selective in- hibitor of CYP17, and EPI-001, a novel compound that interfe- res with the transactivation domain of the androgen receptor are currently being studied in abiraterone- and enzalutamide-resistant prostate cancer patients.

Over the next several years, we can look to the poten- tial devel- opment of predictive biomarkers to inform cli- nicians regarding optimal drug selection, in combination with prospective data generated from randomized trials to better enable optimal man- agement of patients with mCRPC.

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REFERENCES
2. Chang KH, Ercole CE, Sharifi N. Androgen metab-