The Urology Perspective on Expanding Androgen-Targeted Treatments for Men With Castration-Resistant Prostate Cancer

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This is an exciting time for physicians who care for patients with advanced prostate cancer, and more importantly a time of heightened optimism for these men and their families.

Since 2010, six new agents have been approved by the US Food and Drug Administration (FDA) for castrate-resistant prostate cancer (CRPC), including sipuleucel-T, cabazitaxel, abiraterone acetate, denosumab, enzalutamide, and radium-223.[1] With the exception of cabazitaxel, all of these agents are commonly available for both urologists and oncologists to prescribe. In particular, the new oral hormonal agents are especially appealing for urology use given that urologists have been on the forefront of androgen deprivation therapy (ADT) for more than 75 years.[2]

In their review in this issue of ONCOLOGY, Bastos and associates have very nicely summarized the concept that prostate cancer growth is initially highly dependent on circulating androgens[3]; however, in patients whose cancer progresses, androgen-independent pathways become increasingly important drivers of the disease.[4] Although ADT has long been known to improve survival and offers excellent prognosis, over time a significant proportion of patients lose responsiveness to surgical or medical castration (ie, they develop CRPC). CRPC is associated with significant morbidity and mortality, and more than 85% of patients develop painful bone metastases. While the goals of treatment for CRPC include improving survival and mitigating disease progression, these aims must be balanced with the patient's quality of life.[5] CRPC is a heterogeneous disease in which patients generally present with rising prostate-specific antigen (PSA) levels. These men may have nonmetastatic disease, asymptomatic metastatic disease, or symptomatic metastatic disease. Therefore, current treatment options for CRPC require a multidisciplinary approach involving urologists, radiation oncologists, and medical oncologists, as well as nurses and other allied health professionals.

Bastos et al focus their discussion primarily on abiraterone acetate and enzalutamide, speculating that future genetic profiling of androgen receptor alterations may enable better sequencing of these and other agents, as well as facilitating tailored therapy.[3] In the post-docetaxel setting, the clinical and survival benefit of abiraterone and enzalutamide are comparable, and crossover resistance limits the efficacy of each agent when the other is used first. In the pre-chemotherapy setting, abiraterone is FDA-approved based on an approximate
8-month radiographic progression-free survival (PFS) benefit and a 5.2-month increase in median overall survival (OS) (35.3 months with abiraterone + prednisone vs 30.1 months with placebo + prednisone). This survival outcome translated to a 20% reduction in risk of death (hazard ratio [HR] = 0.792; 95% confidence interval [CI], 0.655–0.956; \( P = .0151 \)). Interestingly, this 5.2-month OS benefit was not technically statistically significant based on the trial design of examining the data three times.[6] As of July 2014, enzalutamide is not yet FDA-approved for pre-chemotherapy use, although a 2013 company press release (from Astellas Pharma US) reported both a radiographic and an OS benefit to the drug, prompting the data safety monitoring committee to recommend an unblinding of trial participants with crossover to active drug in the placebo arm. At the American Society of Clinical Oncology’s Genitourinary Cancers Symposium in early 2014, the PREVAIL data were presented, showing a 2.2-month OS benefit with enzalutamide compared to placebo (32.4 months vs 30.2 months), with a median follow-up of 22.3 months and 516 deaths (30% of the study population). This OS difference was statistically significant.[7] The Table summarizes drugs shown to have an OS benefit in CRPC.

In the setting of CRPC, there are many unanswered questions. I have highlighted a few key questions and provided my opinions about each of them:

**Question:** In early pre-chemotherapy metastatic CRPC, how should the novel oral hormonal agents be sequenced? Put another way, once enzalutamide is FDA-approved in the pre-chemotherapy space (which is likely to happen), should we use abiraterone or enzalutamide first?

**Answer:** The correct academic answer is that we do not know. There are some patients who may be better suited for one of the two agents rather than the other. For example, the diabetic patient may be better suited for treatment with enzalutamide, to avoid low-dose steroids; in contrast, a patient with a seizure disorder may be better suited for therapy with abiraterone. It is unclear how (or whether) to use the OS difference (5.2 months vs 2.2 months) as a basis for making initial treatment decisions. In the PREVAIL trial, about 12% of patients had visceral metastases, compared with no patients in the COU-AA-302 study (Cougar Biotechnology, Inc). In addition, PREVAIL was more recent, so more men received post-trial therapy with novel survival-enhancing agents compared with patients treated in COU-AA-302.

**Question:** Is the activity of these two novel oral hormonal agents synergistic—in other words, will we see a day when enzalutamide and abiraterone are used together?

**Answer:** Currently, we do not know. However, several large trials should answer this question. PLATO (Safety Study of Continued Enzalutamide Treatment in Prostate Cancer Patients) is a phase IV placebo-controlled randomized trial with a planned enrollment of 500 patients globally that will compare enzalutamide + abiraterone + prednisone vs treatment with abiraterone + prednisone, with PFS as the primary endpoint. There is also an Alliance (Alliance for Clinical Trials in Oncology Foundation) trial that will randomize 1,224 chemotherapy-naive patients to enzalutamide alone vs enzalutamide + abiraterone + prednisone. The primary endpoint is OS, and the estimated completion date for the trial is 2019.

**Question:** Once one drug is used, will there be response to the other drug?

**Answer:** Preliminary data indicate that the response to the second drug (whether it be abiraterone or enzalutamide) is of much shorter duration/less robust. This was nicely summarized in the current article by Dr. Bastos et al, which described PSA responses from 8% to 45% and time to progression ranging from 2.7 months to 4.9 months.
**Question:** In the era of healthcare reform and potentially fixed reimbursement for episodes of care, how will these novel (and expensive) therapies fare?

**Answer:** I do not know, but I worry about this as a taxpayer and a citizen. I remember in 1989 when urologists were concerned about the then-new concept of combined hormonal therapy with flutamide and the $500- to $800-a-month price tag. Now we are in a whole new era of costs. On the other hand, I am excited to have more effective treatments to offer my patients.

**Question:** How will use of these new oral agents impact the use and efficacy of systemic chemotherapy such as docetaxel and/or cabazitaxel?

**Answer:** Data from PREVAIL show that chemotherapy can be delayed from 10.8 months with placebo to 28 months with enzalutamide (a 17.2-month difference). In COU-AA-302, the delay to chemotherapy in the prednisone + placebo arm was 16.8 months compared with 26.5 months with abiraterone + prednisone. So, we know that chemotherapy will be delayed when these agents are used. However, it remains unclear if chemotherapy will be less effective if it is given after the first line of novel oral therapy. One concern is that urologists may hold on to their patients too long, thereby missing a window of opportunity for effective chemotherapy use. While I feel strongly that urologists can and should use the new agents, I also believe in a multidimensional approach and encourage urologists to work with oncologists to avoid missed opportunities for optimal sequencing.

Indeed, these are very exciting times in the management of CRPC. Stay tuned!

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**References:**


