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RESEARCH HIGHLIGHT

Abiraterone acetate for prostate cancer: a new era of hormonal therapies

Emmanuel S Antonarakis

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Therapies targeting the androgen receptor (AR) axis have constituted the Holy Grail in the management of advanced prostate cancer for seven decades.[1] These hormonal therapies have traditionally taken two main forms: those that suppress gonadal androgen synthesis (e.g., the gonadotropin releasing hormone agonists/antagonists, such as leuprolide), and those that inhibit the AR directly (e.g., the anti-androgens, such as bicalutamide). However, although the vast majority of patients with prostate cancer initially respond favorably to androgen-ablative therapies (manifested by tumor regressions and symptomatic improvements), all patients will eventually develop further disease progression after a median of 18–24 months. This transformed disease state, known as castration-resistant prostate cancer (CRPC), is invariably fatal.

Until recently, life-prolonging therapies for patients with metastatic CRPC (mCRPC) were limited, and consisted only of docetaxel (Taxotere) chemotherapy[2] (U.S. Food and Drug Administration (FDA)-approved in 2004 as first-line chemotherapy for mCRPC). However, in 2010, two additional modalities were added to our armamentarium of FDA-approved treatment options for men with mCRPC: the autologous immunotherapy product sipuleucel-T (Provenge)[3] (indicated for men with asymptomatic or minimally symptomatic disease) and the taxane chemotherapy agent cabazitaxel (Jevtana)[4] (indicated for men progressing after docetaxel). In that same year, the bone-targeting agent denosumab (Xgeva)[5] was also FDA-approved for the prevention of skeletal-related events (bone fractures, spinal cord compression, malignant hypercalcemia, the need for surgery, or the need for radiotherapy) in men with mCRPC, after demonstrating superiority over the bisphosphonate drug, zoledronic acid.

Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD 21231, USA
Correspondence: Dr ES Antonarakis (eantona1@jhmi.edu)

It is now known that androgen signaling remains active even in patients with CRPC, and that the AR is a critical mediator of the transition to the castration-resistant state. One mechanism by which CRPC maintains AR signaling is by overexpressing CYP17, a key enzyme in extra-gonadal (adrenal, prostatic and intratumoral) androgen biosynthesis. In the 26 May 2011 issue of the *New England Journal of Medicine*, de Bono and colleagues[6] reported the results of a multicenter phase 3 trial evaluating the oral CYP17 inhibitor abiraterone acetate (1000 mg daily, administered together with prednisone 10 mg daily) compared against placebo and prednisone in men with mCRPC with progression after prior docetaxel chemotherapy. The trial met its primary end point, demonstrating a 35% reduction in the relative risk of death among men receiving abiraterone compared to those receiving placebo, with a median survival of 14.8 versus 10.9 months respectively ($P<0.0001$). In addition, when compared against placebo, abiraterone treatment resulted in more frequent reductions in prostate-specific antigen (PSA) level by $\geqslant 50\%$ (29% *vs.* 6%; $P<0.0001$), more frequent objective radiographic responses (14% *vs.* 3%; $P<0.0001$), longer time to PSA progression (defined as a $\geqslant 25\%$ PSA increase from nadir) (10.2 *vs.* 6.6 months; $P<0.0001$) and longer radiographic progression-free survival (5.6 *vs.* 3.6 months; $P<0.0001$). Additional data presented at the 2011 American Society of Clinical Oncology Annual Meeting showed that treatment with abiraterone prolonged the time to the first skeletal-related event (10.0 *vs.* 5.0 months; $P=0.0006$) and also provided pain relief and a delay in the time to pain progression (9.4 *vs.* 4.6 months; $P=0.0019$).[7] The results of this trial led to the FDA-approval of abiraterone acetate on 28 April 2011 for the treatment of men with mCRPC who had received prior docetaxel-containing chemotherapy, the second drug to be approved in the postdocetaxel setting.[8]

Adverse events related to abiraterone acetate were generally tolerable, and consisted mainly of a feedback syndrome of secondary mineralocorticoid excess resulting in fluid retention/peripheral edema (31%), hypokalemia (17%) and hypertension (10%). Notably, these toxicities had been more prevalent in prior studies of abiraterone monotherapy, suggesting that these effects were partially mitigated by the concurrent administration of a corticosteroid (i.e., prednisone). Thirteen percent of abiraterone-treated men developed mild cardiac toxicities (mainly tachycardia, or atrial fibrillation). It is therefore recommended that abiraterone be used with caution in patients with a history of cardiovascular disease, symptomatic heart failure, or a left ventricular ejection fraction of $<50\%$. In addition, elevated liver transaminases were observed in 10% of abiraterone-treated patients; two-thirds of these cases were grade 1 events. Abiraterone is contraindicated in patients with severe liver failure, and should be administered at a reduced dose (250 mg daily) in men with moderate hepatic impairment. For patients who develop hepatotoxicity during treatment, abiraterone should be held until recovery of the transaminitis, and treatment may be reinitiated at a reduced dose once hepatic function has resolved. Therapy should be discontinued permanently in men who develop severe hepatotoxicity.

How does abiraterone compare to high-dose ketoconazole (600–1200 mg daily), a non-selective competitive inhibitor of CYP17? Although ketoconazole has not demonstrated a survival benefit in men with mCRPC,[9] it is still commonly prescribed (although not

FDA-approved) for this indication. The efficacy of ketoconazole in the docetaxel-refractory setting has only been examined in retrospective studies,[10] where PSA responses ($\geqslant$50% PSA reductions) have been observed in approximately 25% of patients. Although this figure is almost comparable to that seen with abiraterone in the current study, the toxicities of ketoconazole are more unfavorable and include fatigue, anorexia, emesis, cutaneous effects, peripheral neuropathy and significant transaminitis. Importantly, a recent prospective trial aimed to discern the role of abiraterone in men with mCRPC who had previously received ketoconazole.[11] In that study, PSA response rates were seen in 47% of ketoconazole-pre-treated patients, although those patients were all chemotherapy-naive. This suggests that abiraterone retains activity even in the ketoconazole-refractory population.

The FDA's approval of abiraterone acetate will create new treatment opportunities but will also present new challenges. One dilemma will likely revolve around the optimal timing of abiraterone in men with mCRPC. Although the present study was conducted in docetaxel-pre-treated patients, there is no reason to believe that abiraterone would not be as (or more) effective in chemotherapy-naive patients,[12] and this hypothesis is currently being tested in an ongoing placebo-controlled phase 3 trial in chemotherapy-untreated men. Although a common conceptual framework for understanding mCRPC relates to defining disease states before and after chemotherapy administration, an alternative approach is to describe mCRPC in terms of metastatic burden and disease-related symptoms. To this end, designing trials based on amount of disease burden (or even expected survival as determined by prognostic nomograms), rather than by chemotherapy status, may be a more rational way to examine novel prostate cancer therapies moving forward.

In conclusion, the observation that treatment with abiraterone can prolong survival in men with castration-resistant prostate cancer provides a proof of principle that even this form of the disease remains androgen-driven, and paves the way for a new era of AR-targeted therapies for prostate cancer. As several novel androgen-modulating therapies (e.g., orteronel, MDV-3100, TOK-001 and ARN-509) enter clinical trials,[13] the new challenge will be to determine how to optimally sequence or combine these agents with one another or with other established or experimental treatments for advanced prostate cancer. In addition, the role of abiraterone and other AR-directed therapies in men with earlier disease states is currently undefined. Hopefully, the next decade will shed some light on some of these questions.

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