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Is abiraterone acetate well tolerated and effective in the treatment of castration-resistant prostate cancer?

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SUMMARY

This Practice Point commentary discusses the findings of the first phase I trial to evaluate abiraterone acetate (an inhibitor of the androgen-regulating enzyme CYP17) in the treatment of castration-resistant prostate cancer. This open-label, dose-escalation study by Attard *et al.* showed that abiraterone was well tolerated but often induced a syndrome of secondary mineralocorticoid excess that improved with eplerenone (a mineralocorticoid receptor antagonist). Abiraterone is a potent suppressor of adrenal androgen synthesis, and produced lasting prostate-specific antigen responses in approximately half of the patients. A few patients had partial regression of distant metastases. Although promising, these results should be interpreted with caution owing to the small sample size and because the study was not primarily designed to examine drug efficacy. Multi-institutional, prospective trials should provide additional information on the tolerability and activity of this compound and further define the population most likely to benefit from this endocrine approach.

Keywords

abiraterone acetate; castration-resistant prostate cancer; CyP17 enzyme; efficacy; tolerability

COMMENTARY

Castration-resistant prostate cancers (CRPCs) are those that develop resistance to gonadotropin-releasing hormone agonists and antiandrogens, and such malignancies are responsible for the majority of deaths from prostate cancer. Treatment options for patients with CRPC are currently limited, and only chemotherapy with docetaxel has been shown to extend survival. Attard *et al.*¹ report data from the first phase I clinical trial that used the novel agent abiraterone acetate to treat men with CRPC. This agent is a selective inhibitor of

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Competing interests

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the microsomal enzyme CYP17, which is important in adrenal androgen synthesis. In this study, 21 chemotherapy-naïve men (median age 69 years) with prostate cancer refractory to standard hormonal therapies (median prostate-specific antigen [PSA] 46 ng/ml) were treated with escalating doses of once-daily oral abiraterone acetate (250, 500, 750, 1,000 and 2,000 mg) in three-patient cohorts. Owing to its maximal pharmacodynamic effect, the 1,000 mg dose was chosen for cohort expansion.

At baseline, seventeen patients (81%) had bone metastases, and none had previously received ketoconazole. No treatment-related, dose-limiting toxicities were seen at any dose. Ten men (48%) developed hypokalemia, and six (29%) developed hypertension. These effects were explained by a syndrome of secondary mineralocorticoid excess, which resolved with use of the mineralocorticoid receptor antagonist eplerenone (50 to 200 mg daily). One patient developed migraine headaches that necessitated interruption of treatment, and one man developed an acute asthma exacerbation that required high-dose steroids. In all patients, abiraterone acetate resulted in increased levels of steroids upstream of CYP17, and suppression of downstream adrenal androgens including testosterone. A decline in serum PSA of 50% that lasted 3 months was observed in 12 patients (57%). The median duration of this PSA response was 379 days (range 69-578 days), although five patients continued to have a response until the end of the study. Resolution of bone metastases was seen in 2 of 17 patients (12%). Four of 15 men (27%) with PSA progression while on abiraterone acetate were salvaged by the addition of low-dose dexamethasone.

The androgen receptor and ligand-dependent androgen receptor signaling are now commonly known to remain active and possibly even upregulated in men with castrate levels of testosterone (<50 ng/dl). Standard hormonal therapies (e.g. gonadotropin-releasing hormone agonists and antiandrogens) inhibit gonadal androgenesis, but do not affect androgen synthesis from adrenal or other extragonadal sources. Suggestions have been made that CRPCs may produce intratumoral androgens autonomously.² In addition, overexpression of the *CYP17* gene has been demonstrated in tumors of men with CRPC.³ For these reasons, abiraterone therapy is a rational approach for this population of patients. This study is important as it is the first published clinical trial of abiraterone, and it establishes 1,000 mg as the optimal dose for phase II evaluations. In this small cohort of patients abiraterone seemed to be well tolerated, and the expected adverse effects of hypokalemia and hypertension were well controlled with eplerenone. Although efficacy was not a primary outcome of this trial (the primary end point was tolerability), these preliminary results demonstrate durable PSA responses and even some partial radiologic responses to treatment. Data from some of the ongoing trials with abiraterone in various populations should provide additional information on the possible short-term and long-term toxicities, and efficacy of this agent.

Ketoconazole (a nonselective, competitive inhibitor of several cytochrome P450 enzymes) has often been employed as second-line hormonal therapy for men with CRPC. Single arm and randomized studies indicate that 30-60% of these patients will have a PSA decline 50%, with a median duration of approximately 5-10 months.⁴ Important adverse effects of this agent include neuromuscular, hepatic, and cardiopulmonary toxicities. How the

toxicities of abiraterone (as well as its drug interactions) compare to those of ketoconazole will be important to establish.

Several trials are currently underway to try to determine the efficacy of abiraterone in different clinical settings (castrate resistant, before and after chemotherapy). Early results from another phase I study of abiraterone in men with CRPC demonstrated that among 19 patients with prior ketoconazole exposure, 53% had PSA responses for a median duration of 21 weeks.⁵ In preliminary data from a phase II trial of abiraterone, 60% of 44 chemotherapy-naïve men, and 40% of 28 docetaxel-pretreated men achieved PSA responses.⁶ Finally, initial reports from a phase II study of abiraterone in metastatic, docetaxel-refractory CRPC indicate that 40% of 35 patients experienced PSA responses;⁷ men with prior ketoconazole treatment were not excluded from this study. A multicenter, phase III, randomized clinical trial (NCT00638690) that will evaluate abiraterone versus placebo in patients with docetaxel-resistant, ketoconazole-naïve, metastatic CRPC is now open for enrollment.

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PRACTICE POINT

In patients with castration-resistant prostate cancer, treatment with abiraterone acetate seems promising in terms of both tolerability and efficacy. Ongoing clinical trials will confirm its role in other clinical settings of prostate cancer, including patients with docetaxel-refractory, castrate-resistant metastatic disease.