

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Abiraterone: Current and Future Use in Prostate Cancer



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H&O What is abiraterone (Zytiga, Janssen Biotech), and in which patients is it indicated?

CR Abiraterone is a potent, selective, and orally available inhibitor of CYP17, the key enzyme in androgen and estrogen biosynthesis. In April 2011, the US Food and Drug Administration (FDA) granted approval for its use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel. There are also studies under way that seek to expand that indication to patients with earlier stages of the disease.

H&O The FDA approval of abiraterone for the treatment of CRPC in the postchemotherapy setting was largely based on the results of the COU-AA-301 trial. Can you please discuss this trial?

CR It was a phase III, randomized, placebo-controlled, multicenter clinical study involving 1,195 patients who had received prior chemotherapy containing a taxane. Abiraterone plus prednisone was administered in 797 patients, and 398 patients received placebo plus prednisone. The primary endpoint of the clinical trial was overall survival. There was a statistically significant overall survival difference between those who received abiraterone plus prednisone versus those who received placebo plus prednisone. The results confirmed an increased patient survival of approximately 35% in the abiraterone plus prednisone group compared with the placebo plus prednisone group (14.8 months vs 10.9 months, respectively), as well as PSA

declines (38% vs 10.1%, respectively) and increased time to biochemical progression (10.2 months vs 6.6 months, respectively). Results from an updated analysis were consistent with those from the interim analysis, with a 4.6-month difference in median survival between the 2 arms (15.8 months vs 11.2 months, respectively).

H&O What is the safety profile of abiraterone, and why is monotherapy contraindicated?

CR This drug is interesting in that it specifically and potently inhibits the enzymes responsible for androgen synthesis in the adrenal glands. It may also inhibit androgen production in tumors themselves, although that has yet to be definitively proven. The safety profile of abiraterone is affected by the enzymes that are inhibited versus those that are not inhibited. When a patient takes this drug as a monotherapy without prednisone, that fuels a partial inhibition of adrenal steroid synthesis. The brain and the pituitary gland stimulate this partially blocked adrenal gland, and there is actually excess production of the steroids that are not blocked by abiraterone. It creates a deficiency in the androgens and an excess in everything else. The excess in steroid hormones known as mineralocorticoids leads to sodium retention and wasting of potassium by the kidneys. Thus, when taken without prednisone, abiraterone can cause sodium retention, which leads to high blood pressure, and loss of potassium, which can lead to heart arrhythmias. On the other hand, when the drug is taken with prednisone, those risks are significantly minimized. However, there is still a risk for developing hypokalemia and hypertension, and there is also a modest

risk for liver function abnormalities and fluid retention. Although abiraterone monotherapy is unlikely to be safe, we are looking at reducing the dose of prednisone from 10 mg daily to 5 mg daily. For now, the indication remains 10 mg daily for prednisone.

H&O What are some unanswered questions regarding abiraterone's optimal role?

CR As with any new antineoplastic drug, we would like to be able to help predict and identify which patients are more or less likely to benefit from abiraterone. We hope to identify some of the mechanisms of resistance to the drug, and determine whether those mechanisms are targetable with existing therapies. Additionally, we want to know if abiraterone satisfies the hypothesis that it decreases intratumoral androgen production; there is some early work suggesting that it might, but it has yet to be proven.

Another interesting perspective is that the recommended dose of abiraterone is not the maximum tolerated dose, so one question to explore is whether the drug might be more effective in certain individuals at a higher dose. Additionally, abiraterone is a drug whose bioavailability actually increases when taken with food, although the FDA advises that the drug be taken on an empty stomach. Some researchers are interested in continuing to study these issues. Perhaps the biggest unanswered question regarding abiraterone's optimal role relates to its efficacy in earlier stages of prostate cancer, and there is a phase III study under way that will answer that question. Preliminary results from the COU-AA-302 study are expected within the coming year.

H&O Where does abiraterone fit in the context of other emerging therapies?

CR Another important area to explore is the relative efficacies of abiraterone versus MDV3100. Data from the phase III trial known as AFFIRM (A Study Evaluating the Efficacy and Safety of Investigational Drug MDV3100 in Men With Advanced Prostate Cancer) were presented at the 2012 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium, and showed that MDV3100 also achieved a significant improvement in survival in the same patient population. Future work will determine if these drugs should be used in sequence,

or possibly even in combination. For now, how each of these drugs will settle into the clinic and into the market remains unanswered. MDV3100 has the advantage of not requiring concurrent treatment with a steroid, so that is one of its putative advantages over abiraterone.

H&O What are the future directions in treatment with abiraterone?

CR Although the current approval of abiraterone is in the postchemotherapy setting, it needs to be acknowledged that many men with CRPC, and many men who ultimately die of this disease, never receive chemotherapy in the first place. Should abiraterone prove to be efficacious in the prechemotherapy setting, it will bring about the opportunity of secondary therapy for a population of patients who previously were excluded from it. Approximately 50% of patients with prostate cancer receive no treatment beyond hormone therapy, and ultimately succumb to the disease. These patients could theoretically be treated with abiraterone, because it has a much more attractive safety profile than does chemotherapy. Furthermore, the drug could potentially be prescribed by urologists in addition to medical oncologists, which could offer access to a wider range of eligible patients. Data from these phase III studies in the prechemotherapy setting should be available within the next year or so, and we are anxiously awaiting the results.

Suggested Readings

Bryce A, Ryan CJ. Development and clinical utility of abiraterone acetate as an androgen synthesis inhibitor. *Clin Pharmacol Ther.* 2012;91:101-108.

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de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med.* 2011;364:1995-2005.

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