ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Abiraterone in Prostate Cancer

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H&O What is abiraterone? What is its mechanism of action?

CR Prostate cancer is a disease that is driven by hormones, most notably testosterone and related hormones. It is known that standard hormonal therapy for men with prostate cancer loses its effectiveness over time. There are 2 reasons why standard hormonal therapy loses its effectiveness. The first is that the cancer develops the ability to produce its own hormones, and the second is that the final "on switch" for the cancer, which is the androgen receptor, becomes amplified, causing prostate cancer to become more efficient at surviving in a low hormone environment.

Abiraterone (Cougar Biotechnology) is an orally available drug that reduces androgen levels, even in patients who have undergone standard androgen deprivation therapy. Standard luteinizing hormone releasing hormone (LHRH)-based therapy reduces androgens by approximately 90–95%. As prostate cancer progresses through intracrine androgen production, or other means, the effect of lowering testosterone beyond the initial 90–95% becomes more clinically relevant. Abiraterone lowers testosterone by blocking hormone production. Abiraterone is not expected to replace, but to add to, standard LHRH-based hormonal therapy.

H&O In what setting is abiraterone being studied?

CR The initial study for which we have data was conducted in patients who had already received chemotherapy. In this study, abiraterone demonstrated an improvement in survival compared to prednisone. However, most clinicians would agree that abiraterone might see its greatest degree of efficacy in patients who have not yet received chemotherapy. Many patients with prostate cancer, either due to advanced age or comorbidity, do not get chemotherapy even though it is considered the standard of care. Abiraterone is a drug that can potentially be given to these patients and may replace or delay the need for chemotherapy. Currently, all the major studies of abiraterone have been performed in patients with metastatic disease.

H&O What are some important studies with this agent?

CR There are 2 studies of importance. The first is the COU-AA-301 study. This is a phase III, randomized, placebo-controlled trial of abiraterone plus prednisone versus prednisone alone in 1,195 patients with metastatic advanced prostate cancer who had previously received chemotherapy. Abiraterone plus prednisone was administered in 797 patients, and 398 patients received placebo plus prednisone. The results of this trial were presented at the 2010 annual European Society for Medical Oncology meeting. The primary endpoint in this study was overall survival. The findings showed that abiraterone reduced the risk of death by approximately 35% and improved the time to disease progression by approximately 33%. The median survival in patients who received abiraterone was 14.8 months compared to 10.9 months in patients on prednisone alone. A prostate-specific antigen (PSA) response, which was defined as a 50% or higher decrease

from baseline, was observed in 38% of patients versus 10% of patients in the prednisone group. The time to PSA progression was longer in patients receiving abiraterone versus those receiving placebo (10.2 vs 6.6 months).

The second study that examined abiraterone is COU-AA-302. Like the 301 study, this study is also a phase III, randomized, double-blind, placebo-controlled trial in prostate cancer patients with metastatic disease. It evaluated abiraterone plus prednisone versus prednisone alone in chemotherapy-naïve patients. This study is fully accrued and the data are maturing, but they have not yet been presented.

Overall survival was the most important endpoint in study 301. In study 302, progression-free survival (PFS) will be viewed with equal importance as overall survival, because in the prechemotherapy setting, PFS may correspond with a delay in the time to chemotherapy or a delay in the time to switching therapies. In both studies, the dose was 1,000 mg of abiraterone plus 10 mg of prednisone. Further studies evaluating dosing of both abiraterone and prednisone may need to be conducted to optimize therapy with the drug.

Abiraterone is also being investigated in breast cancer. Hormone production in the adrenal glands is such that, even in women, androgens are produced and then converted into estrogens. Thus, the reduction of the available supply of androgens to breast cancer may correspond to a decrease in the production of estrogens, and may result in clinical benefit, but this is exploratory at this point.

H&O What is the side effect profile of abiraterone?

CR There are 2 unique toxicities seen with abiraterone; one is hypertension and the other is hypokalemia. Both were seen commonly in the 301 study. However, grade 3/4 hypokalemia and grade 3/4 hypertension were reported in only 3.8% and 1.3% of the abiraterone-treated patients, respectively. Hypertension is a very treatable condition, so this agent will most likely not be contraindicated in people with hypertension.

H&O Do you think abiraterone will significantly impact prostate cancer treatment?

CR There are an increasing number of options for prostate cancer; however, they all have different mechanisms. We have made significant advances in prostate cancer treatment this year. We have made improvements in chemotherapy, and we have developed a new immunotherapy (sipuleucel-T, Provenge, Dendreon). Abiraterone, however, is a drug that is an improvement on the existing, very effective hormonal therapy paradigm. We hope that abiraterone is going to allow a significant number of patients to have long-term disease control with this novel hormone in "hormone-refractory" prostate cancer.

The question that should be investigated now is whether more studies to optimize the dose and schedule of abiraterone are needed. It will also be important to evaluate whether this drug can be combined with existing therapies, such as chemotherapy, and whether the improvements in clinical outcome can be further enhanced through earlier initiation of the drug, perhaps in concert with standard hormone therapy.

Suggested Readings

de Bono JS, Logothetis CJ, Fizazi K, et al. Abiraterone acetate (aa) plus low dose prednisone (p) improves overall survival (os) in patients (pts) with metastatic castration resistant prostate cancer (mcrpc) who have progressed after docetaxel-based chemotherapy (chemo): results of COU-AA-301, a randomized double-blind placebo-controlled phase III study. *Ann Oncol*. 2010;21(suppl 8): Abstract LBA5.

ClinicalTrials.gov. Abiraterone Acetate in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer. http://clinicaltrials.gov/ct2/show/NCT00887198. Identifier: NCT00887198.

Ryan CJ, Smith MR, Fong L, et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. *J Clin Oncol*. 2010;28:1481-1488.

Danila DC, Morris MJ, de Bono JS. et al. Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer. *J Clin Oncol*. 2010;28:1496-1501.

Reid AH, Attard G, Danila DC, et al. Significant and sustained antitumor activity in post-docetaxel, castration-resistant prostate cancer with the CYP17 inhibitor abiraterone acetate. *J Clin Oncol*. 2010;28:1489-1495.