Abiraterone increases survival in metastatic prostate cancer

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Biosynthesis of extragonadal androgen may contribute to the progression of castration-resistant prostate cancer. Abiraterone acetate is a selective inhibitor of androgen biosynthesis that acts by inhibiting cytochrome P450 c17, a critical enzyme in testosterone synthesis, and thereby inhibiting androgen synthesis by the adrenal glands and testis and within the prostate tumor. In 2011, abiraterone was approved by the Food and Drug Administration for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received previous chemotherapy containing docetaxel.[1,2]

The approval of abiraterone was based on results of a multicenter, double-blind phase 3 trial in which 1,195 patients with metastatic castration-resistant prostate cancer who had previously received docetaxel were randomized (2:1) to receive abiraterone 1,000 mg (n = 797) or placebo (n = 398), along with prednisone 5 mg twice daily.[1] Treatment could be continued until disease progression. The patients had to have evidence of disease progression (consecutive elevations of prostate-specific antigen [PSA] level above a reference value or radiographic evidence of progression in bone or soft tissue), and Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and an albumin level of or more than 3.0 g/dL. Patients were excluded if they had AST (aspartate aminotransferase) or ALT (aspartate aminotransferase) levels ≥ 2.5 times the upper limit of normal; patients with liver metastases with AST or ALT levels ≤ 5 times the upper limit of normal were permitted in the study. The primary outcome measure was overall survival (OS).

The study patients had a mean age of 69 years, with 28% aged ≥75 years in both groups. The abiraterone and placebo groups were well matched for disease location (bone, 89% and 90%, respectively), Brief Pain Inventory-Short Form pain score (median, 3.0 in both groups), ECOG performance status (0-1, 90% and 89%), previous cytotoxic chemotherapy regimens (1 in 70% and 69%; 2 in 30% and 31%), and median PSA level (129 and 138 ng/mL). Most of the patients (67%) had radiographic evidence of disease progression at study entry.

What's new, what's important

The inhibition of androgen biosynthesis by abiraterone acetate prolonged overall survival in patients with metastatic castration-resistant prostate cancer who previously received chemotherapy. The mechanism of action of abiraterone is inhibition of 17-alpha-hydroxylase/C17,20-lyase (CYP17A1), an enzyme, which is expressed in testicular, adrenal, and tumor tissues. CYP17 catalyzes 2 reactions: the conversion of pregnenolone and progesterone to their 17-alpha-hydroxy derivatives by its 17-alpha-hydroxylase activity, and the formation of dehydroepiandrosterone and androstenedione, by its C17,20-lyase activity. Since, DHEA and androstenedione are androgens and precursors of testosterone, inhibition of CYP17 activity by abiraterone decreases levels of testosterone.

The dose of abiraterone acetate is 1,000 mg given orally, once daily in combination with prednisone 5 mg, which is administered orally twice daily. It must be taken on an empty stomach and no food should be taken for at least 2 hours before the dose of abiraterone acetate is taken and for at least 1 hour after the dose. The most common adverse reactions (≥ 5% of patients) are joint swelling, hypokalemia, edema, muscle discomfort, hot flushes, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, fractures, and upper respiratory tract infection. It has been associated with elevated aminotransferase levels and requires frequent monitoring of liver function during the first 12 weeks of treatment. Abiraterone acetate is a very promising option for patients with castrate-resistant prostate cancer, who progressed on chemotherapy.

— Jame Abraham, MD

The median duration of treatment was 8 months in the abiraterone group and 4 months in the placebo group, and the median duration of follow-up in the total population

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was 12.8 months at the time of a preplanned interim analysis. Data that were unblinded after this analysis showed that OS was significantly longer in the abiraterone group, with the survival differences between the two groups meeting the prespecified criteria for study termination. Median OS was 14.8 months in the abiraterone group, compared with 10.9 months in the placebo group, which represented a reduction of 35% in risk for death (hazard ratio [HR], 0.65; 95% CI, 0.54-0.77; $P < .001$). The benefit of abiraterone on OS was consistent across all patient subgroups (Figure). On multivariate analysis, the significance of the treatment effect (abiraterone vs placebo) on OS remained robust (HR, 0.66; $P < .001$) after adjustment for stratification factors that were also associated with a significant survival difference (ECOG score of 0 or 1 vs 2, pain present vs absent, 1 vs 2 prior chemotherapy regimens, and only PSA evidence of progression vs radiographic evidence). An updated OS analysis (performed when the number of deaths reached the trial's original prespecified threshold of end point events) showed that abiraterone continued to be associated with a significant reduction in risk for death, consistent with the interim analysis (median OS, 15.8 vs 11.2 months; HR, 0.74; 95% CI, 0.64-0.86).[2]

With regard to secondary end points, abiraterone treatment was associated with a greater confirmed PSA response rate compared with placebo (29% and 6%, respectively, $P < .001$), a greater objective response rate among patients with measurable disease at baseline (14% and 3%, $P < .001$), a 42% reduction in risk for PSA progression (median time to progression, 10.2 and 6.6 months; HR, 0.58; $P < .001$), and a reduction of 33% in risk for progression on the basis of radiographic evidence (median progression-free survival, 5.6 and 3.6 months; HR, 0.67; $P < 0.001$).[1]

Common adverse events of any grade in abiraterone patients were also generally prevalent in placebo patients, including fatigue (44% and 43%, respectively), back pain (30% and 33%), nausea (30% and 32%), arthralgia (27% and 23%), constipation (26% and 31%), bone pain (25% and 28%), and vomiting (21% and 25%). Urinary tract infection was significantly more common in abiraterone patients than in placebo patients (12% and 7%, $P = .02$). The most common grade 3 or 4 adverse events in abiraterone patients compared with placebo patients were fatigue (abiraterone: 8% [grade 3], < 1% [grade 4]; placebo: 9% [grade 3], 1% [grade 4]), anemia (abiraterone: 6% [grade 3], 1% [grade 4]; placebo: 6% [grade 3], 2% [grade 4]), and back pain (abiraterone: 6% [grade 3], < 1% [grade 4]; placebo: 9% [grade 3], < 1% [grade 4]). Adverse events resulted in discontinuation of study treatment in 19% of abiraterone patients and in 23% of placebo patients. Adverse events resulted in death in 12% of abiraterone patients and in 15% of placebo patients. Death, primarily from disease progression, occurred within 30 days of the last dose of study medication in 11% of abiraterone patients and in 13% of placebo patients.

Adverse events that were related to elevated mineralocorticoid levels because of CYP17 blockade were significantly more common in abiraterone patients than in placebo patients (55% and 43%, respectively; $P < .001$), including fluid retention and edema (31% and 22%, $P = .04$; mostly grade 1 or 2 peripheral edema), and hypokalemia (17% and 8%, $P < .001$). Cardiac adverse events (primarily grade 1 or 2) occurred in 13% of abiraterone

How I treat castration-resistant prostate cancer

For men with castration-resistant prostate cancer (CRPC), several key decision nodes will have an impact on my initial treatment decisions in the clinic outside of clinical trial participation, which is encouraged at all stages. The presence of liver metastases or significant pain generally steer me away from initial sipuleucel-T, whereas men with asymptomatic or minimally symptomatic metastatic CRPC are generally considered early for this immunotherapy. The emerging data on abiraterone acetate with prednisone prior to docetaxel is compelling, and predocetaxel abiraterone will likely be a standard option for men without visceral disease or major symptoms, while docetaxel or combination trials with docetaxel is considered if these are present. Following docetaxel, abiraterone acetate or cabazitaxel are available, each with prednisone, and decisions are largely empiric because currently we lack predictive biomarkers to allow us to pick one treatment over another. Patient preference, prior treatments, comorbidities, and prior toxicity with chemotherapy will inform upon this decision. However, my goal is for each patient to be able to receive all active therapies that have been approved by the food and Drug Administration during his lifetime, ideally also with clinical trial participation if available, and with a continuous focus on bone health, exercise if feasible, financial toxicity, quality of life, and adequate palliation through radiation, radiopharmaceutics, and bone-targeted agents such as denosumab or zoledronic acid. Men with CRPC are now living many years and should be given the access to all of these new and effective therapies.

— Andrew J. Amrstrong, MD

patients and in 11% of placebo patients, and included tachycardia (3% and 2%) and atrial fibrillation (2% and 1%); there was no difference in frequency of fatal cardiac events between the two groups (1.1% and 1.3%). Abiraterone has been associated with elevated aminotransferase levels, and a grade 4 elevation early in the study led to a protocol amendment that required more frequent monitoring of liver function during the first 12 weeks of treatment. The frequencies of liver function test abnormalities of any grade in abiraterone and placebo patients were 10% and 8%, respectively, and grade 3 or 4 abnormalities (3.5% and 3.0%) were similar in the two groups, including similar frequencies of elevated AST (1.4% and 1.6%) and elevated ALT (1.0% and 1.1%).

References

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