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PROSTATE CANCER

Abiraterone increases overall survival in men with castration-resistant prostate cancer

Abiraterone acetate can officially be added to the list of treatment options for castration-resistant prostate cancer (CRPC). The results of the phase III trial that led to the FDA approval of abiraterone have been published in the *New England Journal of Medicine*.

Until last year, docetaxel or palliative care were the only options for men with metastatic CRPC. However, in 2010, the results of several pivotal trials resulted in the approval of the nonhormonal treatments sipuleucel-T and cabazitaxel for CRPC.

Unlike these drugs, abiraterone targets the androgen synthesis pathway. It is now accepted that castration, either medical or surgical, is not a definitive treatment for prostate cancer, owing to the extratesticular production of androgens. Abiraterone blocks the CYP17 enzyme, disrupting testosterone biosynthesis in the testes, prostate, adrenals and in the tumor itself.

Phase I and II trials of abiraterone showed promise, with between 60% and 70% of patients experiencing a decline in serum PSA level of at least 50%, and a decline in PSA of ≥90% in many recipients. The addition of prednisone helped to overcome resistance to abiraterone in one-third of patients. Adverse effects associated with the drug were mainly attributable to an expected mineralocorticoid excess, and included hypertension, hypokalemia and edema, all of which were successfully controlled by treatment with a mineralocorticoid receptor antagonist. Notably, these early studies included patients who were chemotherapy-naive.

The phase III, randomized, double-blind, placebo-controlled trial, conducted by Johann de Bono and colleagues and known as COU-AA-301, included 1,195 men from 13 countries, who had previously received docetaxel chemotherapy, but whose disease had progressed. Participants were randomized to receive 1 g abiraterone daily in four divided doses plus 5 mg prednisone twice daily, or four placebo tablets daily plus twice-daily prednisone. The primary end point was overall survival from time of randomization, with secondary end points of ≥50% reduction in serum PSA level from the pretreatment baseline, time to PSA progression and radiographic evidence of progression-free survival.

Results were first presented at last year's European Society for Medical Oncology Congress, and showed that patients who received prednisone with abiraterone had a 35.4% reduction in the risk of death compared with those in the placebo group. The median survival duration in patients who received abiraterone was 14.8 months, compared with 10.9 months in those assigned to placebo, an increase that was robust even after multivariate analysis.

Although a 4-month increase in survival seems modest, this statistically significant prolongation of life is impressive in comparison with the outcomes of other strategies. In fact, the increase in survival was judged to be so significant that the trial was prematurely unblinded, so that all patients included in the trial could benefit. The effect of abiraterone on the secondary end points was also very positive, with abiraterone-treated participants experiencing a 29% PSA response rate, compared with 6% in patients who received placebo. Time to PSA progression was also increased and abiraterone was associated with a 42% reduction in the risk of disease progression as defined by PSA concentration. Adverse effects of abiraterone treatment included a slightly elevated risk of urinary tract infection and symptoms of mineralocorticoid excess, especially edema.

The results of the abiraterone trials signify a paradigm shift in our understanding of prostate cancer pathophysiology, as it had previously been believed that tumors became unresponsive to hormonal manipulation upon progression to a castration-resistant state. The abiraterone data illustrate that the androgen pathway remains a target for treatment, even in men with advanced disease.

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In April 2011, following the early release of these results, the FDA approved abiraterone as a second-line treatment for CRPC in men who had experienced disease progression despite having received chemotherapy. However, phase I and II trials of abiraterone, alone and in combination with prednisone, also showed antitumor activity in patients who had not previously received chemotherapy. A further phase III trial is underway to determine whether abiraterone should also be available as a first-line treatment for men with CRPC. Although it will be some time before the results of this study are available, abiraterone—along with other hormonal treatments in development, such as the androgen receptor antagonist MDV3100—is certainly an exciting prospect for the future of CRPC management.

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Original article de Bono, J. *et al.* Abiraterone and increased survival in metastatic prostate cancer. *N. Engl. J. Med.* **364**, 1995–2005 (2011)