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PROSTATE CANCER

An enzalutamide antiandrogen withdrawal syndrome

New research has shown, for the first time, that discontinuation of enzalutamide treatment elicits an antiandrogen withdrawal syndrome (AAWS) response in a small minority of patients with metastatic castration-resistant prostate cancer (mCRPC).

> “[AAWS] was seen in one patient, beginning 40 days after enzalutamide discontinuation”

Prostate cancer is initially sensitive to androgen deprivation therapy (ADT), but ultimately progresses to CRPC. Although CRPC is resistant to ADT, androgen signalling persists, and antiandrogens can further delay disease progression. Resistance to antiandrogens is thought to develop via mutations in the androgen receptor that cause antiandrogens to act as partial receptor agonists. When resistance occurs, discontinuation of antiandrogen treatment can remove the acquired stimulus, resulting in the AAWS, which is characterized by a temporary reduction in PSA levels.

The AAWS has been seen with both steroidal and nonsteroidal antiandrogens, and has now been demonstrated with enzalutamide, a nonsteroidal antiandrogen that significantly improves survival in patients with mCRPC that progresses following docetaxel chemotherapy. In a retrospective study of 30 consecutive patients with mCRPC treated with enzalutamide after docetaxel, PSA levels were measured every 2 weeks following discontinuation of enzalutamide. AAWS, defined as a decline in PSA by ≥50% from the last on-treatment level and confirmed ≥3 weeks later, was seen in one patient, beginning 40 days after enzalutamide discontinuation. Partial responses of 30–50% PSA reduction were seen in two further patients, and the remainder all had raised PSA levels.

Univariate analysis on this small group of patients did not identify any variables that were significantly associated with AAWS. The patient with confirmed AAWS had prolonged treatment of 21.4 months and PSA decline ≥50% with enzalutamide prior to progression and discontinuation. A similar association between antiandrogen response, treatment duration and AAWS has previously been described for bicalutamide. However, the two patients with partial responses had short enzalutamide treatments with no PSA response, so further studies will be required to evaluate any potential link.

Although no impact on survival has been shown for AAWS, symptomatic benefits have been reported. However, the main benefit of AAWS could be its contribution to the understanding of the mechanisms leading to castration resistance, enabling the development of improved mCRPC treatments.

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Original article Rodriguez-Vida, A. *et al*. Is there an anti-androgen withdrawal syndrome with enzalutamide? *BJU Int*. doi:10.1111/bju.12826