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Activity of Abiraterone Acetate in the management of Cushing syndrome associated to advanced adrenocortical carcinoma: results of the ABACUS trial.

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Background: More than 50% of adrenocortical carcinomas (ACC) in adults are associated with cortisol excess that makes tumor management challenging and has a negative impact on patient outcome. Abiraterone acetate (AA) is an irreversible inhibitor of the 17α-hydroxylase/C17, 20-lyase (CYP17 enzyme) that is used in patients with prostate cancer, in whom it leads to suppression of cortisol and androgens. Thus, the drug is potentially useful in the medical treatment of steroid-secreting tumors. The aim of this study was to assess the activity of AA to control cortisol excess in patients with advanced ACC and overt Cushing syndrome. **Methods:** We designed the phase II trial ABACUS (NCT 03145285) whose primary endpoint was normalization of 24-h urinary free cortisol (UFC) excretion within 1 month from treatment start. Inclusion criteria were histologically proven ACC, locally advanced or metastatic disease, and Cushing syndrome confirmed by two 24-h UFC >1.5 times the upper normal limit with suppressed ACTH. No concomitant treatment with mitotane or chemotherapy was allowed for the first 4 weeks of the study. AA was given orally at the daily dose of 1000 mg. **Results:** From 2017 to 2019, we included 17 patients with ACC (2 stage III, 15 stage IV), 13 women (76%), median age 51 years (18-76), of whom 8 have been heavily pretreated and 9 were treatment naïve. In 8 patients, multiple steroid secretion was found. Patients were treated with AA for a median of 17 days (7-163). Median 24-h UFC (measured by gas-mass spectrometry) was 368 μg/24h (121-7422) at baseline and 94 μg/24h (20-1793) at end of treatment (p=0.01). Normalization of 24-h UFC was attained in 8 patients (53%) and a >50% decrement in 11 patients (73%). The median time to effect was 21 days and median 24-h UFC reduction 81.8% (-97.7 - +25.9). Androgen and precursor steroids were also significantly reduced by AA treatment. The median Cushing Syndrome Score was 5.0 (2 - 8) at baseline and 3.5 (1 - 6) at the end of treatment, thus confirming clinical improvement. Blood pressure was significantly reduced and hypokalemia was not observed. In 2 patients, treatment was discontinued for toxicity. Seven patients died of ACC progression during follow-up with an overall survival of 5.4 months (0.5-39.3). **Conclusions:** AA was able to control rapidly cortisol excess in most patients with a good safety profile. The results of this proof-of-concept study show that AA looks promising and may be viewed as an additional weapon to manage Cushing syndrome in patients with ACC. These findings pose the basis for power calculation and implementation of a prospective long-term study to establish AA efficacy in patients with a steroid-secreting ACC.

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