

A phase II trial of abiraterone acetate (AA) without prednisone in castration resistant prostate cancer (CRPC): Results of circulating mineralocorticoid and androgen levels.

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Background:

AA blocks CYP17 and suppresses adrenal androgens and glucocorticoids. Given the risk of mineralocorticoid excess (ME), AA is administered with corticosteroids. In this phase II multicenter, single-arm study, we assess the safety of AA without steroids in CRPC. The primary objective is to determine the proportion of men requiring prednisone to manage ME. Secondary objectives included assessment of androgen and mineralocorticoid serum concentrations and correlating levels with the development of symptoms of ME.

Methods:

Eligible patients had CRPC with controlled blood pressure (BP) (<140/90 on ≤3 agents) and a normal or ≥3.5 mmol/L potassium. Patients initially received AA (1000 mg daily) alone. Patients who developed a BP ≥ 140/90 were treated with anti-hypertensives (HTN) and/or a mineralocorticoid antagonist (MA) prior to steroids per protocol algorithm. Hypokalemia was treated with supplementation or a MA. Patients with persistent or severe ME were initiated on prednisone (5 mg twice daily). To assess PSA response to steroids, prednisone was added to AA at PSA progression. AA therapy was continued until radiographic progression, toxicity, or withdrawal. Serum hormone levels were obtained at baseline, cycle 2, and treatment discontinuation. Mass spectrometry was used to measure serum hormone levels.

Results:

60 patients were enrolled of whom 58 received treatment. 51 (83%) had metastases and 16 (27%) received prior chemotherapy, 6 (10%) prior enzalutamide, and 4 (7%) prior ketoconazole. 38 patients (66%) developed any grade (G) hypertension (48%, n=28), hypokalemia (26%, n=15) and/or edema (20%, n=11). 12 patients (21%) developed G3-4 hypertension (G3 n=8, 14%; G4 n=1, 2%) and/or hypokalemia (G3 n=4, 7%; G4 n=0). There was no G≥3 edema. 9 patients (15%) initiated prednisone for toxicity: HTN (n=3, 5%), hypokalemia (n=4, 7%), fatigue (n=2, 3%). As expected, AA resulted in a reduction in circulating androgen levels and an increase in mineralocorticoids. Lower baseline serum 17-hydroxyprogesterone, dehydroepiandrosterone (DHEA), androstenedione, and androsterone serum levels correlated with the development of any G ME (Table 1).

Conclusions:

In CRPC, AA without steroids is feasible, however clinically significant AEs, particularly hypertension, can occur in a minority of patients. Hypertension and hypokalemia can be treated with anti-hypertensive agents or potassium without steroids in the majority. Baseline circulating serum hormone levels may potentially serve as a predictive biomarker for the development of any grade ME. Use of AA without prednisone needs to be balanced with the potential risk of toxicity.

Table 1. Association of baseline hormone levels with the development of any grade ME.

Hormone	Any G ME	N	Median (ng/mL)	P-Value
17-Hydroxyprogesterone	No	20	0.13	0.03
	Yes	38	0.09	
DHEA	No	20	1.54	0.03
	Yes	38	0.73	
Androstenedione	No	20	0.39	0.04
	Yes	38	0.28	
Androsterone	No	20	0.07	0.01
	Yes	38	0.04	

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