A phase II trial of abiraterone combined with dutasteride for men with metastatic castration-resistant prostate cancer.

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Background: Despite the proven efficacy of abiraterone in metastatic castration resistant prostate cancer (CRPC), disease progression occurs in nearly all individuals. In this study, we evaluated the effect of more complete androgen synthesis blockade with abiraterone, a CYP17A1 inhibitor, and dutasteride, a type I and II 5-α reductase inhibitor, in metastatic CRPC. The primary aim was to investigate mechanisms of resistance to combination therapy.

Methods: Eligible metastatic CRPC patients underwent a baseline metastasis biopsy. Patients received abiraterone and prednisone for two 4-week cycles. After this time, high-dose dutasteride (3.5 mg daily) was added. Patients continued therapy until study withdrawal or radiographic progression. Repeat metastasis biopsy was obtained at progression. Tissue was assessed for androgen receptor (AR) and AR splice variant-7 (ARV7) expression. In cases with adequate tumor, RNA was examined by RNA-seq and assessed for expression of AR regulated genes. Serum hormone and abiraterone levels were assessed.

Results: Forty patients were enrolled. Median PSA at therapy initiation was 28.8 ng/mL and declined to a nadir of 6.3 ng/mL, 3.2 months after therapy initiation. Twenty-four patients (60%) achieved a ≥50% reduction in PSA at a median of 1.4 months. Thirty-two patients experienced PSA progression at a median time of 5 months from therapy initiation and 32 patients experienced radiographic progression at a median time of 11 months. Nearly all baseline (n=29/31) and treatment discontinuation (n=16/16) tumor samples tested for AR nuclear staining were positive. In all positive cases, nuclear staining was more intense than cytoplasmic staining. A subset of patient samples was stained for ARV7: 48% of baseline tumors (n=10/21) and 42% of therapy discontinuation tumors (n=5/12) were positive for ARV7 staining. AR activity, based on an AR regulated gene signature score, in the baseline biopsies were comparable to those in untreated primary tumors from the TCGA data set. Significantly, while AR activity was decreased in most of the matched progression biopsies, this decrease was modest and AR regulated gene expression was markedly higher than in a series of non-prostate or neuroendocrine prostate cancers. At therapy discontinuation, abiraterone levels were lower than in prior cycles in 19 patients (48%). Patients with decreased abiraterone levels were accompanied by a statistically significant decrease in pregnenolone and progesterone and a trend towards an increase in dehydroepiandrosterone-sulfate (DHEAS). Though median DHEAS was reduced from baseline (50,110.0 ng/dL), levels were detectable at higher amounts compared to other androgens at therapy discontinuation (500.0 ng/dL).

Conclusions: Despite increased androgen synthesis inhibition, we demonstrate that the AR axis remains important in disease progression. We highlight that abiraterone metabolism and pharmacokinetics may play a role in resistance. The non-comparative design limits conclusions on the efficacy of dual therapy, but the results support development of further multifaceted approaches towards AR inhibition.

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