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Androgen decline and outcome in castration resistant prostate cancer(mCRPC) patients treated with docetaxel (Doc), prednisone1/-bevacizumab (B)

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Background: Androgen levels are associated with overall survival (OS) in mCRPC. Doc impairs microtubules and has AR inhibitory effects. This analysis evaluates change in androgen levels (Testosterone (T), Androstenedione (A) and DHEA (D) and outcome in Doc-treated mCRPC patients.

Methods: Data from 1,050 men treated on CALGB 90401 with Doc, prednisone and either B or placebo were used. Pre-treatment, 6 week and progression serum assays for T, A and D were performed via tandem Liquid Chromatography-Mass Spectrometry (LC-MS/MS). Ratio of change in androgen (6 week value /baseline value) was calculated. Decline was further evaluated as high or low ($>$ or $<$ median decline for all patients). The logistic regression and proportional hazards models were used to assess the prognostic significance of changes in T, A, and D in predicting PSA response, PFS and OS adjusting for known prognostic factors.

Results: Median values for baseline T, A, and, D were 1.0, 13.5 and 8.1, ng/dL respectively, while androgen levels at 6 weeks were 0.64, 7.0 and 6.8, ng/dL respectively. At 6 weeks a decline in all three androgens was observed. The ratio of 6weeks/baseline in T, A and D were 0.93, 0.56 and 0.86, respectively. There was interaction between levels of T decline and treatment arm (p-value=0.047). Among 291 patients with high levels of T decline, those who also received B were more likely to experience a $\geq$ 50% decline in PSA (87%) compared to those who did not receive B (67%,). Associations between androgen decline and PFS were NS. In multivariable analysis adjusting for prognostic factors, the hazard ratio (HR) for OS demonstrated that decline in T at 6-weeks/baseline was associated with longer OS, HR 1.02 (95% CI 1.01 ,1.03 p = 0.001). Median OS for low T change (ratio $>=$0.93) is 20.9 mos vs 26.3 mos for high T change ($<$0.93).

Conclusions: Patients treated with Doc who experience a greater drop in T on therapy experience a significantly longer OS and higher rate of PSA decline but no effect on PFS. B and androgen decline may confer interacting beneficial effects. Data are consistent with the favorable prognostic significance of higher serum androgens in the CRPC setting and reflecting the potential effect of Doc on AR signalling.

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