

**COMBINATION THERAPY OF ETHINYLESTRADIOL AND ESTRAMUSTINE PHOSPHATE REINTRODUCES OBJECTIVE CLINICAL RESPONSES IN PATIENTS WITH ANDROGEN ABLATION REFRACTORY PROSTATE CANCER (EARLY EXPERIENCE)**

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**Introduction:** Therapy for advanced PCa centers on suppressing systemic androgens and blocking activation of the androgen receptor. Despite anorchid serum androgen levels, nearly all patients develop castration-resistant disease. We hypothesized that ongoing steroidogenesis within prostate tumors and the maintenance of intratumoral androgens may contribute to castration-resistant growth. We evaluated whether a combination therapy of ethinylestradiol and estramustine phosphate can reintroduce objective clinical responses in patients with metastatic CRPC.

**Materials and Methods:** 12 patients (Gleason 8, 9 and 10) with stage D3 disease and bone metastases who had progression despite initial responses to combined androgen blockade and in whom antiandrogen withdrawal subsequently failed, received ethinylestradiol 2mg and estramustine 420 mg daily. PSA, ECOG performance status and bone pain scores were assessed. Median follow-up was 17 months (range 8-26).

**Results:** All cases (90%, 95% CI 55.5-99.8) had an objective clinical response, defined as a greater than 50% PSA decrease (median 87.1%, range 50.2%-94.4%). PSA normalization (less than 4ng/ml) was achieved in 3 cases. All patients reported significant and durable improvement in bone pain (median duration 17.5mon) and performance status (median duration 18mon). The most important side effects were: vein thrombosis (3pz) and gastric pain (2pz).

**Conclusion:** It is now proven that CRPC is sensitive to androgens and moreover could become hypersensitive to androgens low levels and it is finally established that this cancer produces androgens by itself.

For the future the therapy could be: increasing estrogen dose and/or using new androgen antagonist (abiraterone acetate, MDV300?).

Intracrine androgen synthesis produces a "relative hormone-refractariety" and is the new research frontier.