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REVIEW

Overview of enzyme inhibitors and anti-androgens in prostatic cancer

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Surgical castration and estrogen therapy for prostate cancer were developed in 1941, and have been shown to improve both quality of life and survival. Little change in the therapeutics of prostate cancer has occurred over the subsequent three decades. In the 1970s, the progestational anti-androgens, ketoconazole and flutamide, were introduced as androgen-blocking agents, and have been shown to block at least partially both adrenal and testicular androgens. Gonadotropin-releasing hormone (GnRH) agonists were shown in the 1980s to produce medical castration without the cardiac and cerebrovascular risks of standard dose estrogen. In the 1980s, large-scale, multicenter, double-blind studies were done to compare the effect of combined androgen blockade, using multiple drugs, to single-drug blockade of gonadal androgen with regard to time to progression and survival in stage D2 cancer. These studies were done to test theories regarding the role of adrenal androgens and their effects on androgen-sensitive tumor clones in prostate cancer. The theory of clonal heterogeneity, particularly with regard to androgen sensitivity, has led to the continuation of three major controversies about the management of prostate cancer: Is combined blockade of testicular and adrenal androgens in stage D2 prostate cancer more effective than gonadal androgen blockade alone? What is the optimal secondary or tertiary therapy for relapsed prostate cancer? Is there any advantage for combined androgen blockade at the start of therapy in stage D2 prostate cancer as compared to sequential therapy with blockade of testicular androgens first, and then adrenal androgens at the time of relapse?

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