Current concepts in androgen deprivation therapy – is there a “best” endocrine treatment?

Abstract  Androgen deprivation therapy has become the mainstay treatment for locally advanced and metastatic prostate cancer. Castrate testosterone levels can be achieved by a multitude of treatments. We performed a medline literature search to answer the question, is there a “best” endocrine treatment? In conclusion we found that the “best” endocrine therapy for advanced prostate cancer is complete androgen blockade (CAB) with a luteinizing hormone-releasing hormone (LHRH) agonist and a nonsteroidal antiandrogen.

Since the discovery of the hormonal susceptibility of prostate cancer by Hodgkin and Hodges in 1941, hormonal ablation therapy has remained the standard treatment for locally advanced and metastatic prostate cancer [9]. With the decreasing popularity of surgical castration, multitudes of agents capable of achieving castrate testosterone levels have emerged. For clinicians to choose the best agents for medical castration, a thorough understanding of the mechanism of action, efficacy, and side-effect profile for each medication is required.

In response to stimulation with luteinizing hormone-releasing hormone (LHRH), the Leyding cells in the testicle produce testosterone. LHRH secretion is pulsatile in fashion and regulated by the hypothalamic secretion of gonadotropin-releasing hormone (GNRH) over the hypothalamus. The adrenal glands can also produce adrenal androgens that can impact on prostate-cancer growth. Inside the prostate-cancer cell, testosterone is converted to dihydrotestosterone (DHT), the active intracellular form of testosterone, by 5-α-reductase. Agents have been developed that can block any part of this pathway, resulting in single-agent or combination therapies aimed at obtaining medical castration.

Drugs used in medical castration

Estrogen

The principle mechanism of action of estrogen is inhibition of the release of LHRH from the hypothalamus. In addition, estrogen receptors are present in the prostate, especially in the prostatic stroma. It remains uncertain as to whether the very modest amount of estrogen receptors in the prostate could account for any therapeutic action of estrogen on prostate-cancer cells. Side effects encountered during estrogen therapy include hyperpigmentation, increased frequency of migraine headaches, hypertension, water retention, and increased frequency of cholelithiasis and gallbladder disease. Diethylstilbestrol (DES) has been associated with an increased risk for cardiovascular and thromboembolic complications such as deep-vein thrombophlebitis, pulmonary embolism, and heart attacks. These cardiovascular side effects, seen in men using the standard dose of DES (5 mg/day), were unknown before the report by Melinger in 1967 [19]. A 36% increase in non-cancer-related deaths in the estrogen-treated group as compared with the non-estrogen-treated group was observed in this study [17]. Increased cardiovascular morbidity was observed in patients treated with low-dose estrogen as well (DES, 3 mg and 1 mg). Gynecomastia is seen in 40% of cases; it can be prevented by low-dose irradiation to the breasts before the initiation of treatment with DES.
Antiandrogens

Two classes of antiandrogens are available in clinical practice: steroidal and nonsteroidal. Both classes of antiandrogens act by competing with androgen at the androgen-receptor hormone level. In addition, steroidal antiandrogens possess progesterone-like action.

Steroidal antiandrogen

Cyproterone acetate (CPA) was the first steroidal antiandrogen introduced into clinical practice. Among all other derivatives, CPA is the drug most widely used in Europe and other countries to treat prostate cancer. CPA is not commercially available in the United States. It has dual action, inhibiting both the androgen receptor at the cellular level and the secretion of gonadotropin. As a result, levels of testosterone, DHT, estradiol, and LH are decreased [16].

CPA is completely absorbed from the gastrointestinal tract; maximal drug concentrations are achieved at 3–4 h following oral administration. This agent has a half-life of 30–40 h, and a steady-state drug concentration is reached after 8–10 days. It is eliminated via the urine (30%) and bile (70%). The recommended dose of CPA is 50 mg given twice daily, which can be increased to a maximum of 100 mg given three times daily. The disadvantage of CPA in young patients is loss of libido and potency in approximately 86% of patients. Gynecomastia has been seen in 13% of patients. Patients do not report the hot flushes, lethargy, or inability to concentrate that follow surgical or chemical castration. Cardiovascular adverse effects have been encountered, but to a lesser degree than that reported for DES [20]. Hepatotoxicity has been reported; monitoring of liver-function tests, adrenal function, and blood glucose levels is warranted. CPA given at doses of 50–100 mg/day has been shown to be effective in preventing hot flushes as well as the flare phenomenon.

Nonsteroidal antiandrogens

The main advantage of pure antiandrogens is the preservation of libido and potency, probably as a result of an increase in levels of testosterone, DHT, estradiol, and LH.

Flutamide was the first pure antiandrogen to be developed. The drug is rapidly absorbed from the gastrointestinal tract and is extensively metabolized to 2-hydroxyflutamide, which is the active substance. It is almost exclusively eliminated through the urine. Its half-life is 5–6 h. As a pure antiandrogen, flutamide is free of cardiovascular side effects and has no negative impact on carbohydrate or lipid metabolism. The main side effects are painful gynecomastia, abnormal liver function, diarrhea, and gastrointestinal disturbances that lead to patients’ noncompliance and discontinuation of the treatment [6]. The recommended dose for flutamide monotherapy is 250 mg given orally three times daily. Similar to the other antiandrogens, flutamide is effective in preventing the flare phenomenon associated with LHRH agonists.

Nilutamide differs from flutamide only in its lateral side chain. Following oral intake the maximal plasma concentration of nilutamide is reached after 2 h. Its half-life is 56 h, which is longer than that of flutamide; thus, the drug can be recommended for once-daily dosing (150 mg). Potential side effects are alcohol intolerance, reactions similar to those described for disulfiram (reported in up to 5% of patients), a decrease in the speed of dark/light adaptation, and interstitial pneumonitis that can progress to pulmonary fibrosis. However, in most cases these side effects are readily reversible upon discontinuation of the drug.

Bicalutamide has a long half-life and is 5–10 times more potent than flutamide. The most common side effect is breast tenderness and gastrointestinal side effects. Bicalutamide can displace the coumarin anticoagulant warfarin from its protein-binding sites, and prothrombin time should be closely monitored in patients concomitantly receiving an oral anticoagulant. The drug has been tested as monotherapy at three different doses (50, 100, and 150 mg), which appear to be equally effective.

LHRH agonists

LHRH analogs came into use in the late 1970s and provided a medical form of castration for advanced prostate cancer. Although naturally occurring LHRH stimulates LH release and supports its circadian cycle, it has been demonstrated that synthetic LHRH agonists lead to the suppression of LH and of testosterone production to castrate levels following the initial phase [1]. They have been found to be as efficacious as DES and bilateral orchietomy [15].

One of the side effects resulting from LHRH treatment is the flare phenomenon secondary to stimulation of LH and testosterone secretion during the first 2–3 weeks of treatment. This phenomenon can be accompanied by clinical symptoms such as increased bone pain. Treatment with an antiandrogen prior to the initiation of LHRH agonist therapy is often prescribed to prevent such side effects.

LHRH antagonists

These agents are direct antagonists of the LHRH receptor and suppress androgen production. Their early use was associated with release of histamine and anaphylaxis leading to death. New agents are being investigated that cause LHRH blockade but lack these potentially dangerous side effects.