The Current State of Hormonal Therapy for Prostate Cancer

Beth A. Hellerstedt, MD; Kenneth J. Pienta, MD

Dr. Hellerstedt is Fellow, Division of Hematology and Oncology, University of Michigan Medical Center, Ann Arbor, MI.

Dr. Pienta is Professor, Internal Medicine and Urology and Director, Urologic Oncology Program, University of Michigan Medical Center, Ann Arbor, MI.

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ABSTRACT Androgen deprivation therapy remains a mainstay of treatment for men with prostate cancer. New uses for hormonal therapy, including use in the adjuvant and neoadjuvant setting, are being evaluated. Prevention of the side effects of therapy has led to the development of alternative schedules and therapeutics. *(CA Cancer J Clin 2002;52:154-179.)*

INTRODUCTION

Hormonal or androgen deprivation therapy is utilized in multiple settings in the prostate cancer patient (Figure 1). In general, androgen deprivation induces a remission in 80 to 90 percent of men with advanced prostate cancer, and results in a median progression-free survival of 12 to 33 months.[1] At that time, an androgen-independent phenotype usually emerges, leading to a median overall survival of 23 to 37 months from the time of initiation of androgen deprivation.

In 1895, White first documented the use of androgen ablation in 111 men with prostate hypertrophy treated by castration.[2] David and colleagues isolated testosterone in 1935 and in 1941, Huggins and Hodges introduced androgen deprivation as therapy for advanced prostate cancer.[3,4] In the 1950s, retrospective analyses provided data suggesting that patients treated with hormonal therapy in the form of estrogens or orchiectomy enjoyed a survival and quality-of-life advantage when compared with patients followed in the pre-therapy era.[5,6]

Multiple strategies have been used to induce castrate serum levels of testosterone or interfere with its function (Figure 2). In order to rigorously test the previously reported data that androgen deprivation can impact the natural history of prostate cancer, the Veterans Administration Cooperative Urological Research Group (VACURG) conducted three large, randomized studies regarding the treatment of early stage and advanced prostate cancer from 1960 to 1975.[7,8,9,10] These prospective studies provided data on a large cohort of men, and provided guidelines for the use of orchiectomy and estrogens as treatment. In the 1980s, luteinizing hormone-releasing hormone (LHRH) agonists and antiandrogens were introduced. These compounds have been evaluated in practically every conceivable clinical setting, from the traditional role in advanced disease to use in the adjuvant and neoadjuvant settings. Combination treatment with testicular androgen suppression and an antiandrogen (called combined androgen blockade or maximal androgen blockade) soon followed. Although an impressive body of knowledge has accumulated, the variety of options and occasionally conflicting data has made the use of hormonal therapy all but straightforward.

METHODS OF PRIMARY ANDROGEN ABLATION

Orchiectomy

The first VACURG study, published in 1967, randomized 1,764 Stage III and IV patients to one of four treatment options: placebo, orchiectomy plus placebo, DES 5 mg per day, or orchiectomy plus DES 5 mg per day.[8] Orchiectomy was associated with a one-year survival rate of 73 percent and a five-year survival rate of 35 percent in Stage IV patients, compared with 66 percent and 20 percent in placebo-treated patients. With longer follow-up, however, overall survival curves for all four arms were equivalent, suggesting that the type of hormonal treatment did not influence the development or course of androgen-independent disease.[11] Compared with placebo, all treatments were associated with subjective improvements in pain and performance status.

Despite data regarding its efficacy, orchiectomy may be an underused form of hormonal treatment. Surgical castration is an outpatient procedure that results in an immediate reduction in circulating testosterone over a period of a few hours.[12] Although data are sparse, some studies suggest that up to 50 percent of men choose orchiectomy when it is offered as an option for reasons of convenience and cost.[13] The most recent data from the Prostate Cancer Outcomes Study provided an update on quality-of-life issues for patients receiving hormonal therapy.[14] Men who chose LHRH agonist therapy reported greater problems with their overall sexual functioning than did orchiectomy patients, despite both groups having similar levels of function prior to treatment. LHRH agonist patients were also less likely to perceive themselves as free of cancer, due to the need for ongoing injections. Another study, however, suggested that men who underwent orchiectomy were more likely to regret this decision as compared with those treated with LHRH agonist therapy.[15]

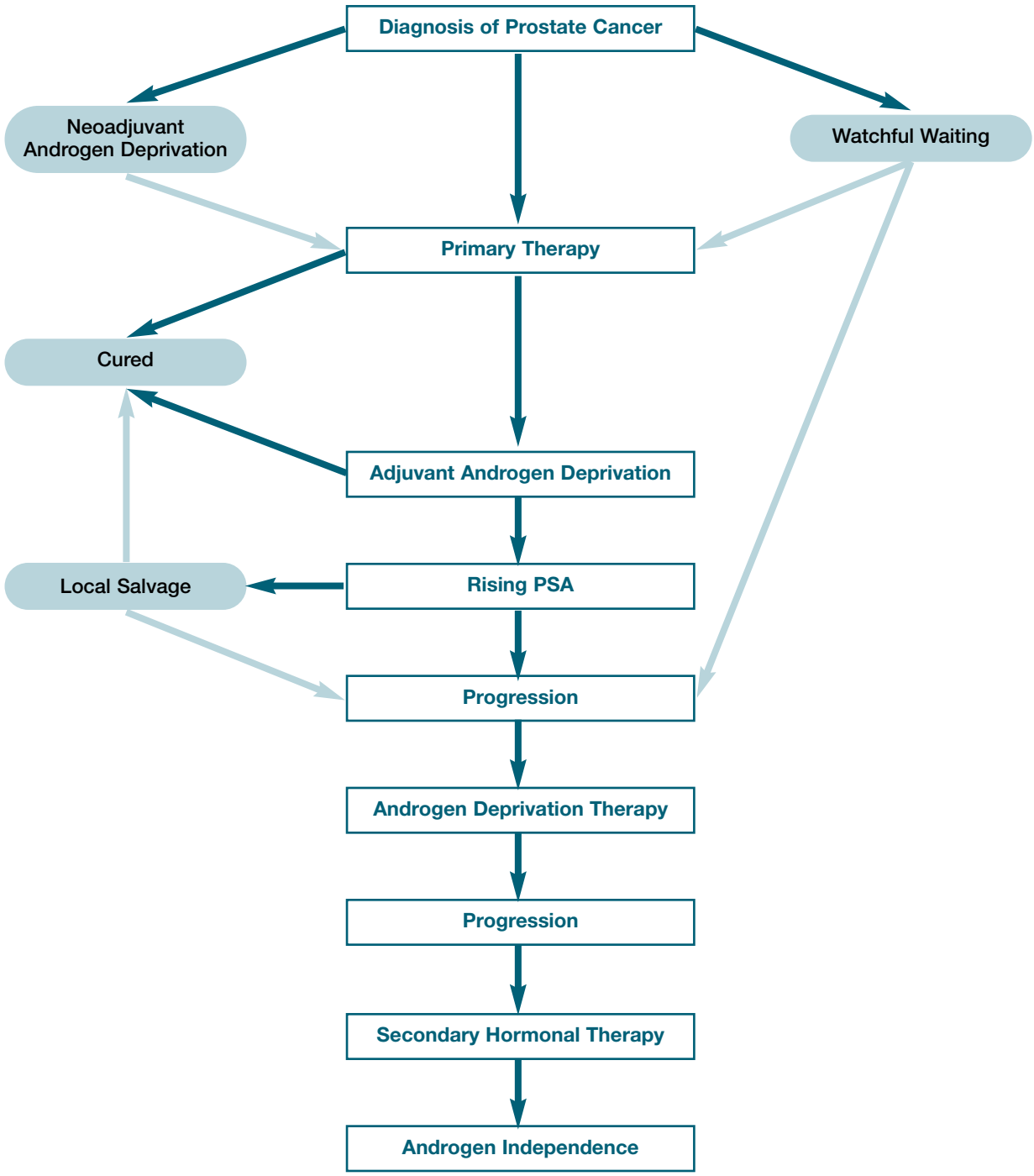
Diethylstilbestrol

Diethylstilbestrol (DES), a semi-synthetic estrogen compound, was one of the first nonsurgical options for the treatment of prostate cancer. Widespread use has been limited, however, by the potential for significant cardiovascular and thromboembolic toxicity.

Initial studies from VACURG and the European Organization for Research and Treatment of Cancer (EORTC) used 3 to 5 mg of DES per day, and showed the remission rate of DES to be equivalent to orchiectomy.[8] Overall mortality, however, was higher in the DES group due to an excess of cardiovascular deaths. A more recent study (EORTC 30805) demonstrated the equivalence of orchiectomy and DES at 1 mg per day.[16] In this study, 13 percent of patients receiving DES had treatment discontinued due to cardiovascular complications, compared with none in the orchiectomy arm. Most of the events were venous in nature, including edema and deep venous thrombosis. DES at a dose of 3 mg per day has also shown equivalence to LHRH agonists in patients with locally advanced and metastatic disease in terms of overall survival and subjective improvement.[17-21] DES proved to be superior to flutamide alone in the treatment of metastatic disease.[22] Several EORTC trials (30761 and 30762) demonstrated DES 3 mg per day to be equivalent to estramustine[23] and cyproterone.[24] The introduction of the LHRH analogs, with no significant cardiovascular toxicity, lack of

FIGURE **1**

Treatment Algorithm After Initial Diagnosis



After initial diagnosis, patients have several options regarding treatment. Androgen deprivation therapy is indicated, however, at the time of disease progression after definitive and salvage local therapy.

breast enlargement, and significant reimbursement for clinicians, essentially ended the use of DES as a first-line hormonal therapy. DES is no longer mass produced for human use in the United States.

Cyproterone

Cyproterone acetate (CPA) is a steroidal, progestational antiandrogen that blocks the androgen-receptor interaction and reduces serum testosterone through a weak antigonadotropic action.[25] It is commonly used in Canada as monotherapy or as an agent to prevent disease flare during initiation of LHRH agonist therapy. Cyproterone can also suppress hot flashes in response to androgen deprivation treatment with LHRH agonists or orchiectomy.[26] Although it is generally well tolerated, CPA is also associated with a high rate of cardiovascular complications, and is not available in the United States.

LHRH Agonists and Antagonists

The introduction of the LHRH agonists, the two most common being leuprolide and goserelin, revolutionized the treatment of advanced prostate cancer. No surgery is required—a potentially important physical and psychological benefit.

LHRH is normally released from the hypothalamus in pulses. This leads to the pulsatile release of FSH (follicle stimulating hormone) and LH (luteinizing hormone). LH attaches to receptors on the Leydig cells of the testes, promoting testosterone production. Constant exposure to LHRH after treatment with an LHRH agonist, however, eventually causes downregulation of receptors in the pituitary, inhibition of FSH and LH release, and a concomitant decrease in testosterone production.

Initial treatment with LHRH agonists, however, causes a surge of LH release, with a corresponding increase in testosterone levels. This testosterone surge can result in a transient increase in prostate cancer growth. Some patients can experience a worsening of bone pain, urinary obstruction, or other symptoms attributable to rapid cancer growth, known as the flare phenomenon.

LHRH agonists have different side effect profiles than DES and CPA, including no cardiovascular toxicity. Phase III studies of LHRH agonists versus surgical castration demonstrated no difference in survival between the two therapies.[27] Depot preparations (injections lasting three to four months) for androgen ablation are now the most common treatments for metastatic prostate cancer. Multiple Phase III studies have demonstrated that all preparations have similar efficacy.[28]

Abarelix is one of the new, modified gonadotropin-releasing hormone antagonists. Unlike the standard LHRH agonists, abarelix is a direct LHRH antagonist, and thus avoids the flare phenomenon. This compound was recently compared with leuprolide acetate in a Phase III randomized trial.[29] Medical castration, as measured by serum testosterone levels, was achieved in 75 percent of the abarelix group by day 15, compared with 10 percent of patients in the leuprolide group. The percentage decrease in PSA was significantly greater in the abarelix group on day 15 after treatment. At day 29, post-treatment and beyond, PSA levels were similar between leuprolide and abarelix. As this study does not have mature follow-up, it is not possible to determine if abarelix and leuprolide will provide identical rates of disease control.

PC-SPES

PC-SPES, an herbal supplement, has been evaluated in a prospective Phase II trial.[30] The mechanism behind the efficacy of PC-SPES is not well understood. The toxicities and

biochemical effects appear to be estrogenic. Analysis of the product, however, did not yield any known estrogens. As PC-SPES is an herbal supplement, no standards exist for ensuring all pills have equal amounts of "active" extract. Additionally, PC-SPES has been shown to decrease PSA production in vitro, a finding that may play a role in evaluation of efficacy. Recently the California Department of Health Services (CDHS) found traces of warfarin in PC-SPES during laboratory analysis.[31] Researchers at the University of California/San Francisco Medical Center then issued a statement indicating that certain lots of PC-SPES being used in a clinical trial also contained traces of DES.[32] The CDHS has subsequently recalled all lots of existing drug.[33]

Nonsteroidal Antiandrogens

The nonsteroidal antiandrogens bicalutamide, flutamide, and nilutamide interfere with the binding of testosterone and dihydrotestosterone to the androgen receptor (Figure 2). In a randomized, multicenter trial of 486 patients with previously untreated metastatic prostate cancer, bicalutamide 50 mg per day was compared with castration with either orchiectomy or LHRH agonist therapy.[34] Bicalutamide was almost as effective as orchiectomy; treatment failure occurred in 53 percent of bicalutamide-treated patients compared with 42 percent of castrated patients. Survival was not significantly different between the two groups. Although PSA progression was not considered to be evidence of disease progression, PSA normalization occurred in 17 percent of the bicalutamide group and 47 percent in the castrated group; this represented a median decline of 88 percent and 97 percent from baseline, respectively. The authors concluded that 50 mg of bicalutamide was not as effective as castration for the treatment of patients with metastatic disease. Given this data, antiandrogens, when utilized at conventional doses, do not provide adequate androgen deprivation. Therefore, they should not be used as single agents for the treatment of advanced prostate cancer.

Combined Androgen Blockade

Monotherapy with androgen deprivation results in a decline of 90 percent of circulating testosterone (Figure 2). Ten percent of circulating testosterone is still present in castrated men due to peripheral conversion of circulating adrenal steroids to testosterone.

Few subjects have generated more controversy in the field of urologic oncology over the last ten years than the question of whether patients should be treated with monotherapy versus combined androgen blockade (CAB). CAB consists of treatment with a LHRH agonist or orchiectomy plus a nonsteroidal antiandrogen.

The first trial to show a potential advantage to CAB over monotherapy was published in 1989. This randomized, double blind, placebo-controlled study evaluated leuprolide alone versus leuprolide and flutamide in 603 men with previously untreated, metastatic prostate cancer.[35] CAB was associated with a significant improvement in median progression-free survival (16.5 months versus 13.9 months) and in median overall survival (35.6 months versus 28.3 months). Men with minimal disease and good performance status appeared to benefit the most from combined therapy, although retrospectively, only 41 men in each group qualified for this category. In addition, the use of CAB in initial therapy lessened the flare phenomenon. It was unclear if the prevention of the flare could account for the differences in survival. Testosterone levels were elevated for a few weeks at most. These results were considered to be validated by two other early trials: EORTC 30853[36] (originally reported in

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