Hormonal and Chemotherapeutic Systemic Therapy for Metastatic Prostate Cancer

Ravat Panvichian, MD, and Kenneth J. Pienta, MD

Promising new approaches in the treatment of prostate cancer include gene therapy, tumor-biology-based therapies, and the development of new agents and combination chemotherapy.

Background: Prostate cancer is the most frequently diagnosed cancer and the second leading cause of cancer death in men in the United States. It is estimated that over 300,000 men will have been diagnosed with prostate cancer in 1996, and more than 40,000 will have died of this disease.

Methods: The authors combined their experience with a review of the literature on management of this disease to examine the effectiveness of treatments for both localized and metastatic prostate cancer.

Results: Surgery and radiation therapy are potentially curative modalities for cancer still limited to the gland. Androgen ablation therapy results in stabilization or regression of metastatic disease in most instances but is not curative. Some new approaches are described for patients with hormone-refractory prostate cancer.

Conclusions: Newer tumor-biology-based combinations are promising in the treatment of hormone-refractory prostate cancer, but their effect on patient survival needs to be evaluated in larger clinical trials.

Introduction

Prostate cancer is the most frequently diagnosed cancer and the second leading cause of cancer death in men in the United States. In 1996, prostate cancer will have been diagnosed in approximately 317,000 men and will have caused more than 41,000 deaths.[1] While radiation therapy and surgery are potentially curative treatment modalities for cancer that is still limited to the gland, treatment of metastatic disease remains palliative. In those symptomatic patients with newly diagnosed metastatic prostate cancer, androgen deprivation is the mainstay of treatment. Androgen ablation therapy results in stabilization or regression of the disease in approximately 80% of patients but often fails to prevent progressive disease. Men with progressive prostate cancer in the presence of total androgen blockade are defined as having hormone-refractory prostate cancer (HRPC). In the past, no effective “standard” chemotherapy was available for patients with HRPC, which has a median survival of six to nine months.[2] However, recent developments in basic and clinical research have shown promise in improving the morbidity and mortality rates of patients with HRPC.

Androgen Dependence

The prostate gland is sensitive to a variety of hormones, but androgens are the key components in prostate cellular proliferation and growth throughout a man’s life. The importance of androgens in prostate cancer became apparent in the seminal works of investigators in the 1940s[3-5] when they established the concept of androgen dependence of prostate cancer and demonstrated that surgical castration (orchiectomy) or medical castration (estrogen therapy) produced a reduction in cancer mass and a clinical remission in 80% of patients with advanced metastatic disease. As a consequence, the disruption of the hypothalamic-pituitary-gonadal axis by surgical or medical castration has been the mainstay of therapy for metastatic prostate cancer (stage D1 or D2). In 1960, the five-year survival rates in patients so treated were 20% compared with 0% in placebo or untreated patients.[6]

Role of Androgens in Prostate Biology

Androgens are derived from the testis and the adrenal cortex. Testicular androgens are released by the Leydig cells after stimulation by luteinizing hormone (LH), which in turn is controlled by a pulsatile release of the hypothalamic gonadotropin-releasing hormone (GnRH=LHRH), Testosterone is converted into dihydrotestosterone (DHT) in the peripheral tissues and in the prostate by the activity of the 5-alpha-reductase enzymes. Adrenal androgens are released by the adrenal cortex after stimulation by adrenocorticotropic. These adrenal androgen, mainly composed of dehydroepiandrosterone, its sulfate, and androstenedione, undergo a multistep conversion to testosterone and DHT in the peripheral tissues and in the prostate itself.[7] The binding of androgens, mainly DHT, to nuclear androgen receptors allows
Primary Hormonal Treatment Options

Four major methods of androgen deprivation can be used in the palliative treatment of metastatic prostate cancer: (1) surgical castration by orchietomy to remove the primary androgen-producing organs, (2) medical castration by estrogen therapy or LHRH therapy to reduce LH production, (3) antiandrogen therapy directed primarily at the target organs (ie, prostate and metastatic sites), and (4) combined androgen blockade.

Bilateral Orchietomy

Bilateral orchietomy, the standard by which other forms of hormonal therapy are measured, removes approximately 90% of circulating testosterone and decreases bone pain almost immediately. Thus, surgical castration may be an appropriate choice for patients with aggravated symptoms and impending complications of parasympysis by metastatic disease. Complications are minimal, and the side effects are associated with androgen withdrawal (ie, loss of libido, impotence, and hot flashes). Removal of the testis is a major psychologic aspect associated with orchietomy.

Estrogen and LHRH Therapy

In the treatment of prostate cancer, estrogens exert their effect primarily by a negative feedback at the hypothalamic-pituitary level, which results in reduced LH secretion and testicular testosterone synthesis (Fig 1). Castrate levels of testosterone (less than 50 ng/dL) in patients receiving an oral dose of 3 mg of diethylstilbestrol (DES) daily were achieved in a range of 21 to 60 days.[8] Generally, this dosage of DES is necessary to obtain adequate castrate levels.[9] A dose level of 1 mg daily of DES will lower testosterone to castrate levels in 80% of patients, but its effectiveness varies among individual patients. Doses of less than 1 mg daily of DES do not result in an appreciable decrease in testosterone levels. A regimen containing a dosage level of 5 mg of DES has been associated with thromboembolic toxicity and thus is no longer administered.[10] Adequate dosage of oral estrogen treatment is as effective as orchietomy or an LHRH analog in the treatment of metastatic prostate cancer; however, changes in the blood (eg, increases in platelet aggregation, low-density lipoprotein, and certain clotting factors) that may result in thromboembolic sequelae have tempered enthusiasm for the use of estrogens.

Acute administration of the LHRH analogs stimulates the secretion of LH in the pituitary gland. Conversely, chronic administration suppresses LH secretion by the down-regulation of the receptors in the pituitary, leading to a decrease of plasma testosterone and resulting in a complete and reversible medical castration. The different LHRH formulations share the same properties, and the depot preparations (eg, leuprolide, goserelin acetate) appear to be equally efficacious in controlling prostate cancer when compared with bilateral orchietomy or additive estrogen therapy. A transient worsening of signs and symptoms (tumor flare) during the first week of therapy is a side effect of LHRH analog treatment. This effect is the result of the transitory LH and testosterone surge. The peak increase in serum testosterone occurs within 72 hours, and achievement of castrate levels occurs within four weeks from the initial dose. Antiandrogen administration is recommended before or simultaneously with the first LHRH analog depot injection to prevent tumor flare and its clinical complications in patients with overwhelming metastatic disease.

Antiandrogen Therapy

An antiandrogen is any compound that blocks the interaction between androgens and their receptors in the presence of normal or even increased target tissue levels of DHT. Currently, the primary role of antiandrogens is in combination treatment. Antiandrogens consist of two types: nonsteroidal agents and steroidal antiandrogens with progestational activity. The two progestational antiandrogens -- cyproterone acetate and megestrol acetate -- block androgen receptor function and inhibit the release of LH by their progestational action. As monotherapy, neither compound alone suppresses androgen production completely, and a rise toward normal in plasma testosterone concentration occurs after several months. In general, progestational antiandrogens are not used as initial hormonal monotherapy for patients with metastatic disease.

Nonsteroidal antiandrogens in combination therapy currently receive more attention, particularly in their role in combination therapy to achieve maximal androgen withdrawal. The current pure antiandrogens are flutamide, nilutamide, and bicalutamide, which are all structurally related. They act directly on the prostate cancer cells by competitively blocking the binding of DHT to the nuclear androgen receptor.

Combined Androgen Blockade

While plasma testosterone dramatically decreased by 90% or more following surgical or medical castration, prostate DHT, the major stimulus for prostate epithelial growth, remained at approximately 25% of precastration levels due to the intraprostatic synthesis from the adrenal androgens (Fig 2).[11] Maximal or combined androgen blockade (CAB) is achieved by the central inhibition of androgen production through medical or surgical castration combined with peripheral blockade of circulating androgens by the use of an antiandrogen (eg, flutamide or casodex). A study in support of CAB was conducted by the European Organization for Research of the Treatment of Cancer (EORTC 30853)[12] in which the combination of goserelin and flutamide was compared to orchietomy. Another study from the NCI and the Southwest Oncology Group (SWOG)[13] compared leuprolide with leuprolide plus flutamide. In both studies, patients receiving the CAB showed a survival advantage of approximately seven months. However, several other studies have not shown a measurable difference in outcome between monotherapy and CAB, and a recent meta-analysis of all randomized clinical trials of monotherapy vs CAB reported little difference between the two groups.[14] Given the conflicting data, the benefit of CAB remains unclear. Ongoing studies should clarify this issue.

Early or Delayed Endocrine Therapy

Determining the most effective timing of endocrine treatment of prostate cancer remains controversial. Endocrine therapy is the mainstay of treatment for all symptomatic patients with metastatic prostate cancer, while asymptomatic patients should be evaluated according to their general health and concomitant diseases. A review of data from the Veterans Administration Cooperative Urological Research Group (VACURG) using a covariate analysis suggests that some patients may benefit from early treatment.[15] A survival benefit was seen in younger patients with more aggressive stage D prostate cancers (Gleason score 7-10) when hormonal treatment began at the time of diagnosis, but a follow-up period of at least three years was needed to show differences between the early-treatment group and the
**Intermittent or Continual Therapy**

In experimental studies with the androgen-dependent Shionogi mouse mammary carcinoma, Akakura et al.[16] showed that postcastration progression of tumors to an androgen-independent state was linked to the cessation of androgen-induced differentiation of stem cells resulting from deprivation of androgen. The androgen-induced differentiation of stem cells with recovery of apoptotic potential is the basis for the concept of intermittent androgen-deprivation therapy of androgen-dependent tumors. Several cooperative groups are investigating this theory to determine if temporary interruption of androgen deprivation can delay or prevent the development of androgen independence.

**Prostate-Specific Antigen Level as a Predictor of Treatment Outcome**

Prostate-specific antigen (PSA) is a 34 kDa glycoprotein found in prostatic tissue and seminal plasma. Serum levels of PSA correlate well with extent of disease. Serum PSA has been used to evaluate response to treatment in both hormone-dependent and hormone-refractory disease. PSA can rapidly assess tumor response because of its short half-life of two to four days. After the initiation of hormonal therapy, PSA levels decrease over a period of three to four months. The PSA nadir, representing quiescent disease, lasts approximately 18 to 24 months in the average patient. The PSA level is often the earliest sign of treatment failure or relapse in patients with metastatic prostate cancer who undergo primary androgen ablation therapy. The rise in PSA portends clinical progression by approximately six months. Decreases in baseline PSA with treatment have been shown to correlate with improved prognosis in both hormone-dependent disease and hormone-refractory disease.

In trials of HRPC, a posttherapy decrease in PSA of 50% or more that was documented on multiple determinations and maintained over time (more than six months) was the most significant prognostic factor in predicting prolonged survival.[18] The majority of men with metastatic prostate cancer who are treated with androgen ablation respond initially, thus demonstrating that at least a proportion of their cancer cells are androgen responsive. However, most of these patients eventually relapse to a state that is unresponsive to further antiandrogen treatment, regardless of the aggressiveness of their secondary antiandrogen manipulations. Androgen ablation therapy fails to cure the disease because the prostate cancer in each patient is heterogenously composed of clones of both androgen-dependent and independent prostate cancer cells at the time of first presentation.

A significant proportion of primary and metastatic prostate adenocarcinomas contains a subpopulation of neuroendocrine cells.[19] These prostatic neuroendocrine cells produce a variety of biogenic amines and neuropeptides that can impact on tumor growth and metastatic behavior in a paracrine or autocrine manner.[19,20] Prostatic neuroendocrine cells may contribute to the androgen-independent progression of prostate cancer by clonal expansion or through the paracrine stimulation of adjacent adenocarcinoma. The development of future therapies that use neuroendocrine pathways for therapeutic benefit is promising.

**Management of HRPC**

**Continued Androgen Suppression**

In the past, most patients with metastatic prostate cancer were treated with orchiectomy either as first-line treatment or at the time of failure of primary medical androgen suppression. Thus, these patients who enrolled in trials for HRPC were androgen-deprived. With the availability of medical forms of reversible androgen suppression involving LHRH analogs and antiandrogens, the role of continued androgen suppression has become important. A recent retrospective review[21] from the Southwest Oncology Group (SWOG) concluded that continued androgen suppression was not a significant factor in patient survival. Taylor and colleagues,[22] however, retrospectively analyzed 341 patients from four clinical trials and demonstrated a modest survival advantage for patients on continued androgen suppression. Currently, SWOG policy recommends that patients continue on androgen suppression during chemotherapy trials.

**Flutamide or Antiandrogen Withdrawal**

Flutamide withdrawal syndrome refers to a significant decline in PSA levels following withdrawal of antiandrogen therapy due to evidence of disease progression. This phenomenon was documented in 10 (29%) of 35 patients in whom disease had progressed following combined androgen blockade.[23] The duration of the PSA decline seen with discontinuation of flutamide was short (median = five months), but the decline was associated with symptomatic improvement. The response to flutamide withdrawal may be explained by the presence of functionally altered androgen receptors that recognize flutamide as an androgen agonist or by the unmasking of the agonistic property of flutamide. A similar phenomenon has been seen in case reports of casodex. When disease progression occurs following antiandrogen therapy, observation is recommended to determine the effects of flutamide withdrawal before evaluating subsequent interventions.[23]

**Therapies Based on Tumor Biology**

Currently, no single or combination cytotoxic chemotherapy regimen for HRPC has consistently shown objective tumor regression or prolonged patient survival. However, new therapies for HRPC are being developed that are based on new approaches to cancer therapy rather than the traditional chemotherapeutic targets such as DNA and RNA. These approaches rely on an understanding of dynamic structure and function of cancer cells (ie, cell shape, movement, and signaling). The dynamic structure of the cell is composed of a tissue matrix system that interacts to organize and process spatial and temporal information to coordinate genetic information and cell function.[24] Virtually every part of the tissue matrix system is altered in cancer cell therapy, thus providing the potential for the development of cancer-specific targets. Four chemotherapeutic regimens (suramin, estramustine plus vinblastine, estramustine plus etoposide, and estramustine plus paclitaxel) based on inhibiting dynamic cell structure are being studied in clinical trials of HRPC and appear promising based on results of preliminary clinical studies.

**Suramin**

Suramin, a polysulphonated napthylurea, is the first of a new class of growth factor antagonists with a 55-day serum half-life(T1/2-Beta). Suramin affects not only interactions between growth factors and their respective receptors, but also several cellular functions. It possesses striking antiangiogenesis activity based on its ability to competitively block the binding of fibroblast growth factors (and other growth factors) to their respective transmembrane receptors.

Suramin was evaluated in prostatic cancer on the basis of its inhibitory effects on growth factor-induced proliferation and antitumor activity against human-derived prostatic cancer cell lines, both in vitro and in vivo. The initial trial[25] of suramin in HRPC demonstrated a 35% objective response rate in patients with measurable soft-tissue disease and a 35% response rate based on a decrease in PSA of 75% or more in patients with bone-only disease. Subsequent reports have confirmed the activity of suramin in HRPC (Table 1).[25-29]

![Table 1](image-url)
The overall response to suramin in these trials is 55% using PSA declines of 50% or more and 30% when considering only patients with measurable disease. Its principal side-effects are neurotoxicity and fatigue.

Because suramin therapy can cause adrenal insufficiency, hydrocortisone replacement is needed with suramin therapy. The percentage of the observed response rate to suramin that is due to hydrocortisone coadministration or flutamide withdrawal has recently been questioned. In addition to its beneficial effect on pain palliation from bone metastasis, corticosteroids also cause decreases in PSA levels. Hydrocortisone in physiologic replacement doses can result in a decline in PSA levels to 50% or more in 20% to 50% of patients.[30] These issues are being addressed in ongoing prospective, randomized trials, including a phase III trial comparing suramin plus hydrocortisone with placebo plus hydrocortisone.

**Estramustine and Vinblastine**

Estramustine phosphate consists of an estradiol molecule attached to a nornitrogen mustard through a carbamate ester linkage. Estramustine cytotoxicity is predominantly attributed to its ability to bind microtubule-associated proteins, which are essential to the stability of microtubules.[31] Estramustine causes microtubules to disassemble and prevents their de novo formation, resulting in mitotic arrest during metaphase and the disruption of many vital cellular functions that lead to cell death. Vinblastine is a vinca alkaloid whose cytotoxicity is also attributable to microtubule inhibition, but it acts by binding to the beta subunit of the tubulin monomer, a distinctly separate microtubular target.

Estramustine and vinblastine were combined based on in vitro evidence of additive antimitotic activity and nonadditive toxicity. The major side effect of estramustine is nausea, and the major toxicity of vinblastine is myelosuppression. Three trials were conducted to evaluate the combination of estramustine and vinblastine in the treatment of HRPC (Table 2).[32-34] Based on a decrease in PSA levels of 50% or more, responses in these trials were similar at approximately 50%, and the overall response rate was 30%.

**Estramustine and Etoposide**

The nuclear matrix, the RNA-protein network of the nucleus, plays an important role in DNA replication and gene expression. The DNA matrix attachment site is part of a "replication complex" that includes the topoisomerase II enzyme. Etoposide is a topoisomerase II inhibitor that selectively inhibits DNA replication at the level of the nuclear matrix.[35] In addition to acting as a microtubule-associated protein inhibitor, estramustine also binds to the nuclear matrix.[35]

Etoposide and estramustine interact in a synergistic fashion at the level of the nuclear matrix in both in vitro and in vivo animal models.[35] A clinical trial based on these data was conducted for patients with HRPC in which 50 mg/m2 of oral etoposide daily was combined with 15 mg/kg of estramustine daily for 21 days with cycles repeated at 28-day intervals.[35] In this phase II clinical trial of 42 patients, 18 had measurable soft-tissue disease. Using standard response criteria, nine (50%) of these patients responded (three complete and six partial). Of 24 patients with bone-only disease, 14 (58%) showed a decrease in PSA levels of more than 50%, and bone scans improved in six (25%) patients. The overall response rate was 15 (36%) of the total 42 patients, and 22 (52%) had a decrease in PSA levels of more than 50% (Table 3). A concurrent trial of oral etoposide alone failed to show significant activity.[36]

**Estramustine and Paclitaxel**

Paclitaxel inhibits microtubule disassembly and freezes cells in mitosis. Although neither paclitaxel nor estramustine appeared to have significant single-agent activity in HRPC, Speicher et al.[37] evaluated their combined activity in human prostatic carcinoma cell lines based on the potential complementary mechanisms of action of estramustine and paclitaxel. These investigators demonstrated in vitro the synergistic cytotoxic effect of the estramustine and paclitaxel combination in human prostate cancer cells. Hudes et al.[38] used this information to initiate a phase II trial of estramustine and paclitaxel in 17 patients with HRPC. Ten (58%) of 17 patients demonstrated a decrease of more than 50% in their baseline PSA, and three (50%) of six patients achieved a partial response, suggesting that the combination of estramustine and paclitaxel is an active regimen in the management of HRPC (Table 4).

**Conclusions**

Metastatic prostate cancer remains an incurable illness with multiple factors influencing patient survival. A clearer understanding of the process by which a tumor develops and recurs following treatment has fostered the development of new approaches in the prevention and treatment of prostate cancer (Fig 3, Table 5). New combination therapies based on tumor biology are promising in the treatment of HRPC, although their effects on patient survival must be evaluated in larger clinical trials. Studies are ongoing to investigate strategies such as chemotherapy and radiation therapy or gene therapy to treat the cancer before it metastasizes. Many of the current controversial issues associated with management of metastatic prostate cancer should be resolved in the near future. The next decade should provide us with new weapons by which to attack and defeat prostate cancer.
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References


From the Departments of Internal Medicine (RP) and Surgery (KP) at the University of Michigan Comprehensive Cancer Center, Ann Arbor, Mich. Address reprint requests to Dr. Panvichian at 1150 W Medical Center Dr, 5510 MSRB-I, Ann Arbor, MI 48109-0680.