Clinical Review

Treatment of Advanced Prostate Cancer

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Many patients with prostate cancer present with advanced disease (stage C or D). For these patients, treatment is palliative and is aimed at reducing serum testosterone levels. Since the growth of prostate cancer is testosterone-dependent (approximately 95% of testosterone is produced by the testes, with the remainder coming from the adrenals), hormonal manipulation has been the mainstay of palliative treatment. Bilateral orchiectomy has been the traditional approach, but most patients prefer equally effective drug therapies that include the administration of estrogens, luteinizing hormone-releasing hormone (LHRH) agonists, and antiandrogens.

Key words. Prostate; treatment outcome; disease management; drug therapy; orchiectomy. (*J Fam Pract 1993; 37:488-494*)

Prostate cancer is the most common malignancy in the male population of the United States. Unfortunately, prostate cancer is not diagnosed in many patients until the tumor has progressed to an advanced stage with involvement beyond the prostate (stage C or D). The etiology of prostate cancer is not well understood, but there is a clear association between serum testosterone levels and prostate tissue growth.

The treatment of advanced prostate cancer is primarily palliative, as cures are rare. Bilateral orchiectomy results in castrate levels of testosterone within a few hours of surgery. Modern drug therapy is as effective as surgery, however, and is more acceptable to most patients.[1] Estrogens such as diethylstilbestrol (DES) are effective, but are associated with an increased risk of thromboembolism and cardiovascular complications.[2,3] Luteinizing hormone-releasing hormone (LHRH) analogs produce response rates that are comparable to those seen with DES and orchiectomy but without the cardiovascular complications or potential psychological distress. However, as a result of an initial stimulation of serum testosterone, a "flare reaction" sometimes occurs. Concurrent use of antiandrogens such as flutamide may improve the results seen with LHRH analogs; also, flare reactions diminish with concurrent treatment.

Current research indicates that many patients with prostate cancer want to take a more active role in decision-making with regard to their treatment.[4] Thus, primary care physicians may become more involved in counseling these patients on treatment options.

This paper discusses the treatment options for patients with advanced stage prostate cancer, and highlights some of the new therapeutic strategies for dealing with intractable bone pain.

Diagnosis and Staging

Historically, the "gold standard" for screening for prostate cancer has been digital rectal examination. Despite its almost universal use, however, it has a sensitivity (the likelihood of identifying a condition) of only 69% to 86% and a positive predictive value of only 22% to 31%.[5] Because of the high incidence of advanced disease on initial diagnosis of prostate cancer (40% to 50% of patients have metastatic disease at diagnosis),[1,6] there is great interest in the development of a screening tool for earlier diagnosis. Most research has focused on serum markers used in conjunction with the physical examination. In 1979, Wang et al[7] first identified prostate-specific antigen (PSA),[7] a glycoprotein that appears to be more specific than prostatic acid phosphatase as a tumor

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Table 1. Prostate Cancer Staging

Stage	Description
A	Incidental finding on tissue examination following prostate removal
B	Palpable tumor on rectal examination confined to the prostate
C	Local tumor extension beyond the prostatic capsule involving the seminal vesicles or other tissue
D	Metastatic tumor
D_1	Regional nodes involved
D_2	Bone, lymph nodes above the aortic bifurcation, or other organs involved

Adapted from Crawford ED, Dawkins CA. Diagnosis and management of prostate cancer. Hosp Pract (Off Ed) 1986; 21(3):159–74.

marker, and more accurate for monitoring disease progression.[8] PSA is also a more sensitive index of disease than either digital rectal examination or transrectal ultrasonography.[9]

Patients with malignancy confined to the prostate gland are classified as having stage A or stage B prostate cancer, depending on the histology and whether the finding is made incidentally or clinically. Patients with disseminated disease confined to the periprostatic area are classified as having stage C disease. Those with metastatic disease outside the periprostatic area are classified as having stage D disease. If only pelvic lymph nodes are involved, it is classified as stage D_1 disease, and if bones, lung, or other organ systems are involved, the disease is classified as D_2 (Table 1).[10] Investigations useful in the staging process include a chest radiograph, bone scan (including radiographs of suspect areas), and on occasion, an intravenous pyelogram. Computed tomography of the pelvis is useful in assessing pelvic and periaortic lymph nodes, although lymphadenectomy may be needed. Magnetic resonance imaging can distinguish between benign prostatic hypertrophy and carcinoma, and show the degree of local periprostatic spread.

Endocrine Control of Prostatic Growth

The growth of prostate tissue is dependent on androgenic stimulation. The major circulating androgen in a man is testosterone, approximately 95% of which is produced in the Leydig cells of the testes. The average production rate of testosterone is 6 to 7 mg/day.[11] The usual peripheral serum concentration of testosterone is approximately 600 ng/dL, decreasing to 500 ng/dL after 70 years of age.[11] Bilateral orchiectomy reduces serum testosterone levels to an average of 43 ± 32 ng/dL.[2]

Table 2. Probability of Progression of Prostate Cancer at One Year, by Percent Decrease in PSA

	Decrease in PSA			
Variables	<80%	80%–89%	90%–94%	≥95%
Number of patients	23	5	8	4
Percent of patients progressing	91	80	25	25

PSA denotes prostate-specific antigen.
From Matzkin H, Eber P, Van der Zwaag R, Soloway MS. Prognostic value of pre and post treatment prostatic specific markers (PSA + PAP) in hormonal withdrawal treatment of stage D2 prostate cancer. J Urol 1992; 147:389A. Reprinted with permission.

Testosterone is converted to its active form, dihydrotestosterone (DHT), peripherally or in the prostate or seminal vesicles through the enzymatic action of 5-alpha-reductase.[11,12] The usual peripheral serum concentration of DHT is 56 ± 20 ng/dL.[11]

Testosterone production by the Leydig cells is under control of luteinizing hormone (LH), a glycoprotein secreted by the anterior pituitary gland. The production of LH, in turn, is stimulated by gonadotropin-releasing hormone (GnRH), a hypothalamic decapeptide.[1,12]

To a lesser degree, DHT also derives from the adrenal androgens androstenedione and dehydroepiandrosterone.[6] The controversial role of adrenal-gland–derived androgens provides the basis for total androgen ablation regimens, discussed below.

Treatment of Advanced Prostate Cancer

Because of the close relation between prostate cancer and androgens, hormonal therapy has a major role in the treatment of this malignancy. The use of hormonal manipulation in the treatment of prostate cancer was first evaluated by Huggins et al[13] over 50 years ago. Overall, subjective and objective response rates with hormonal therapy are in the range of 60% to 80%, and last for 18 to 24 months.[1,14] In patients with prostate cancer who had moderately to markedly elevated PSA values (>10 ng/mL) before hormonal therapy, those with a ≥80% reduction in PSA within the first month of treatment had a significantly ($P < .001$) longer period before disease progression than those with lesser reductions in PSA.[15] In another study, 57 patients with stage D_2 prostate cancer were treated with hormonal therapy. A ≥90% reduction in PSA at 3 and 6 months correlated with a prolonged progression-free survival ($P < .001$, Table 2).[16] Similar results were found in another trial after orchiectomy.[17] Thus, hormonal therapy must be regarded as palliative rather than curative, since ultimately,

all patients with advanced prostatic carcinoma treated with hormonal therapy will have progressive disease while undergoing therapy.

Bilateral orchiectomy promptly reduces androgen concentrations, with castration levels reached within 3 hours.[18] However, impotence is universal following this procedure, and the psychological trauma of castration should not be underestimated.[1] Indeed, it is important to note that given the choice, most patients (78%) will opt for equally effective medical alternatives to orchiectomy.[4] Such therapies include estrogens, LHRH analogs, and antiandrogens.

Estrogens

Estrogens block testosterone binding at the hypothalamic level, resulting in a reduction in GnRH release and LH secretion. These drugs also directly inhibit testicular production of testosterone, and reduce the fraction of free circulating testosterone by increasing its protein binding.[1] In the 1960s, the first Veterans Administration Cooperative Urologic Research Group study concluded that hormonal therapy, namely, DES, 5 mg/day, reduced mortality resulting from prostate cancer, but this benefit was attenuated by an increase in mortality from cardiovascular disease.[19] Since a 1-mg dose of DES does not reliably suppress testosterone concentrations to castrate levels,[20,21] 3 mg is the preferred dose.[1] Even given in this amount, however, DES produces cardiovascular side effects in 34% of patients, which is markedly greater than with alternative hormonal therapy.[3,22,23] In one trial, 13 of 53 patients receiving estrogen therapy vs none of 47 undergoing orchiectomy suffered major cardiovascular complications ($P < .001$).[24] Patients receiving DES may also experience water retention, nausea, vomiting, gynecomastia, loss of libido, impotence, infertility, and an increased incidence of thrombotic disorders.[2] Importantly, orchiectomy has been shown to be as effective as DES, with no additive benefit in combining the two modalities of therapy.[14] As a result, DES is no longer recommended by most urologists as primary therapy for metastatic disease.

Luteinizing Hormone-Releasing Hormone Analogs

The introduction of the LHRH analogs has provided an alternative to estrogens and orchiectomy in the treatment of advanced prostate cancer. These agents initially stimulate and then suppress pituitary release of LH through a process called "receptor desensitization." As a result, testosterone levels fall to castrate levels within 7 to 10 days of the start of therapy.[1] Major benefits of LHRH analogs include their safety and ease of administration. For example, depot intramuscular injections can be given safely in the office setting, generally on a monthly basis.

Table 3. Treatment Response to Leuprolide Acetate vs Diethylstilbestrol

Response	Percent of Patients	
	Leuprolide (n = 92)	Diethylstilbestrol (n = 94)
Complete response	1	2
Partial response	37	44
No change	48	39
Progressive disease	11	11
Actuarial one-year survival*	87	78
Side effects†	3	13

**The difference between treatments was not statistically significant.*
†Necessitating withdrawal from study.
Adapted from The Leuprolide Study Group. Leuprolide versus diethylstilbestrol for metastatic prostate cancer. N Engl J Med 1984; 311:1281–6.

The first commercially available LHRH analog was leuprolide acetate. In a comparative trial, leuprolide and DES, 3 mg/day, had similar therapeutic effects (Table 3), but leuprolide had fewer cardiovascular adverse effects.[25] Congestive heart failure, angina, myocardial infarction, or thromboembolic disease occurred in 13% of those receiving DES but in only 4% of those receiving leuprolide. Peripheral edema and gynecomastia were reported in 17% and 50%, respectively, of the patients in the DES group, compared with 2% and 30%, respectively, of the patients receiving leuprolide.[25] Similar objective response rates (such as a decrease in tumor size or metastases or both) are achieved with the daily subcutaneous formulation of leuprolide and the monthly depot formulation (86% and 81%, respectively).[26]

Similar results were obtained by the British Prostate Group in their comparison of DES, 3 mg/day, orchiectomy, and goserelin (Zoladex). Goserelin was comparable to orchiectomy in response rate, survival (115 and 104 weeks, respectively), and the incidence of impotence. Although response rates and survival were comparable between goserelin and DES, the response to treatment was faster in the goserelin group. However, 21% of patients randomized to receive DES withdrew from the trial because of side effects, whereas none of those who received goserelin withdrew.[27] Comparable results were reported by the Zoladex Prostate Study Group, in which objective response rates were between 77% and 84% for combined goserelin and DES therapy, and combined goserelin therapy and orchiectomy, with no significant differences among the groups.[28]

Side effects seen with LHRH analogs include hot flashes, resulting from the profound hypoestrogenic state caused by these agents, and an early flare phenomenon.

The latter is characterized by worsening of symptoms and is caused by the acute increase in serum testosterone concentrations.[29] For example, 3% to 17% of patients receiving an LHRH analog have reported worsening bone pain during the first week of treatment.[25,27,29–32] This flare reaction can be ameliorated by prior and concurrent therapy with DES or flutamide (a nonsteroidal antiandrogen), which blocks adrenal androgen production.[30,31] It is not known how long flare blockade treatment needs to be administered, but as several deaths have been reported coincident with unblocked flare reactions, use of a blocking agent should be considered.[32]

Hot flashes have reportedly occurred in 52% to 76% of men receiving an LHRH analog for prostate cancer.[25,28,33] Hot flashes can be ameliorated with concurrent transdermal estrogen[34] or clonidine therapy.[35,36] Other common side effects include decreased libido and decreased erectile potency, as expected with any hormonal therapy.[29]

Antiandrogens

Antiandrogens fall into two categories: nonsteroidal and steroidal. The nonsteroidal antiandrogen flutamide has been approved for use in combination with LHRH analogs in the treatment of prostate cancer. Its usual dose is 250 mg orally, three times daily. Steroidal antiandrogens include cyproterone acetate, which is not currently available in the United States but is used widely in Europe, and megestrol, which is available but not indicated for the treatment of prostate cancer in the United States.

The use of flutamide as monotherapy has not been extensively studied. In one trial, it was shown to be equivalent to DES, 3 mg/day, with fewer side effects.[37] More recently, the Eastern Cooperative Study Group reported their results with 92 patients with stage D_2 prostate cancer randomized to receive DES, 1 mg, or flutamide, 250 mg, three times daily. Although overall response rates were similar (62% and 50%, respectively), median survival was greater in the DES group (43.2 vs 23.2 months, respectively, $P = .007$).[23] It appears that the optimal role of flutamide is in combination with LHRH analogs, in a strategy known as "total androgen blockade."

Total Androgen Blockade

As noted previously, the testes produce approximately 95% of the total testosterone in circulation. The adrenal glands are responsible for the balance as well as serving as the source of androstenedione and dehydroepiandrosterone.[38] The possibility of further reducing the stimulatory effects of androgens beyond the suppression of testicular production has led to the concept of total androgen blockade.

In 1985, a randomized, double-blind trial, sponsored by the National Cancer Institute, compared leuprolide alone with leuprolide plus flutamide in the treatment of previously untreated patients with stage D_2 prostate cancer. Six hundred three patients were eligible. Although there were no significant differences in the complete or partial response rates between the two groups, combination therapy was associated with a significantly greater median progression-free survival time (16.5 months vs 13.9 months, respectively) and overall survival time (35.6 months vs 28.3 months, respectively). Flare reactions were also reduced in frequency with combination therapy. Among subgroups, it was clear that the greatest benefit of combination therapy was in patients with good performance status and minimal disease.[39]

Recently, the median time to disease progression (58.3 months for combination therapy vs 19.1 months for leuprolide alone) and the median survival time (61 months for combination therapy vs 41 months for leuprolide alone) were reported for patients with minimal disease.[40] These data support the use of combination therapy in patients with stage D_2 prostate cancer and minimal disease (ie, metastases limited to axial skeleton plus pelvic and soft tissue nodal disease).[40]

The International Prostate Cancer Study Group recently reported an analysis of its study comparing goserelin, 3.6 mg by depot injection monthly, given alone and given with flutamide in 547 evaluable patients with advanced prostate cancer. Although there was no significant difference in complete or partial response rates, the group receiving goserelin alone had a significantly longer time to treatment failure (437 vs 351 days). Tumor flare reactions were again reduced in frequency with combination therapy.[41] Although concomitant use of flutamide does reduce the incidence and severity of the flare reaction seen with LHRH analog monotherapy, it is unclear how long flutamide therapy must be given.

Treatment of Hormone-Refractory Prostate Cancer

Unfortunately, hormonal therapy of advanced prostate cancer is palliative since virtually all patients ultimately die of their disease unless there is an intervening cause of death. New treatments for patients whose disease recurs are desperately needed. Chemotherapeutic agents, including cyclophosphamide, doxorubicin, 5-fluorouracil, dacarbazine, cisplatin, estramustine, and streptozocin, alone or in combination, have produced disappointing

overall response rates of approximately 30% (in those with mostly stable disease, with few complete or partial responses), with median survivals of 26 to 33 weeks.[42] In one European trial of 29 patients with advanced, hormone-resistant prostate cancer, single-agent mitomycin C was associated with a total objective response rate of 59% and an actuarial median survival time of 10.8 months.[43] The possibility of combination chemotherapy is a logical extension of the finding of modest activity with several single agents. Combination therapy, however, may offer only slight advantages over sequential attempts with single-agent therapy. In a study of 142 patients with hormone-resistant prostate cancer, the combination of 5-fluorouracil, doxorubicin, and mitomycin C was shown to produce a significantly longer median survival time than sequential treatment with the same three drugs (265 vs 217 days, $P = .025$), but as would be expected, myelosuppression was greater.[44]

Because of the poor survival results noted with chemotherapy in patients with hormone-resistant prostate cancer, the Southwest Oncology Group examined the role of combination hormone and chemotherapy.[45] One hundred thirty-seven patients were randomized to receive hormonal therapy (DES or orchiectomy) followed by cyclophosphamide plus doxorubicin, at disease progression or as combined therapy at the outset. Although combined modality therapy was associated with a somewhat greater response rate (63% vs 48%, respectively; $P = .059$), there was no difference in median survival time (25.6 vs 22.0 months for the initial hormonal therapy group and the chemohormonal group, respectively).[45] Thus, combined modality therapy cannot be recommended at this time.

Suramin, a synthetic polyanionic compound, has been used investigationally in the treatment of hormone-refractive prostate cancer. Its effects may relate to a growth factor inhibitory effect, binding to various proteins (thus inhibiting their action), and to an adrenocorticolytic effect.[46] In two small clinical trials,[47,48] response rates of 53% to 62% have been reported; in the trial reported by Manyak et al,[47] the median survival was 9.7 months. Additionally, significant pain relief occurred in over 70% of patients with pain.[46,47] Despite several toxicities, including nephrotoxicity, hypocalcemia, hypermagnesemia, and a neurotoxic reaction known as demyelinating polyradiculoneuropathy, suramin has a potentially important role in the treatment of prostate cancer.[47,48]

Palliative Care

Unfortunately, many patients with advanced prostate cancer become resistant to hormonal therapy as well as chemotherapy. For these patients, pain management for bone metastases is indicated. Although 35% to 40% of patients receiving hormonal therapy or chemotherapy for prostate cancer report improvement in bone pain,[25,43] the relief may be delayed and incomplete. Additionally, many other patients do not experience any relief. In such patients, palliative treatment with radiation therapy and drugs is indicated. Among the radiologicals that have been demonstrated to produce prompt pain relief are rhenium 186(Sn) (a tin isotope),[49,50] phosphorus 32,[51] and strontium 89.[52] Response rates of up to 87% have been reported.[51] Another type of radiotherapy is hemibody irradiation, either to the upper half or to the lower half of the body. Complete response is obtained in up to 70%, and partial or complete response can be expected in 72% to 100% of patients, generally within 24 hours.[53]

Therapy with intravenous pamidronate[54] or clodronate[55] can provide dramatic improvement in bone pain. Such agents may exert their effect by inhibiting osteoclasts, which decreases osteolysis and facilitates bone healing. However, pain usually recurs when therapy is completed. Thus, analgesics such as narcotics and nonsteroidal anti-inflammatory drugs are indicated. Other symptoms for which palliative hormonal therapy is useful include anorexia and symptoms of urinary obstruction.

Summary

Prostate cancer is the most common cancer in American men. Unfortunately, in many cases, diagnosis is not made until the disease has progressed. Treatment of advanced prostate cancer is primarily hormonal. Within this category, the LHRH analogs, especially leuprolide and goserelin, have demonstrated the greatest promise, producing survival rates that are at least comparable to those of DES or orchiectomy and with fewer side effects. These drugs can be administered safely in an office setting. The primary care physician is in the ideal position to discuss the treatment options with the patient and assist him in decision-making.

The role of total androgen blockade (combining orchiectomy, DES, or an LHRH analog with flutamide or another antiandrogen) is controversial, but there appears to be a role for such aggressive treatment in patients with stage D_2 prostate cancer and minimal disease. Chemotherapy is used in hormone-resistant cases, but objective response rates are low, and median survival time is less than 10 months. The focus of therapy is palliative, and analgesic care is needed, especially in patients with bone metastases. In addition to the objective response rates of hormonal therapy and chemotherapy,

over one third of patients will also have significant pain relief. Other approaches such as the use of radiologicals and hemibody radiation therapy can provide prompt, marked, and lasting pain relief.

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