Current Pharmacological Treatment Options for Prostate Cancer

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ABSTRACT
Prostate cancer is the most prevalent male cancer and is the second leading cause of cancer-related death in men. Advances in screening through digital rectal examinations and prostate-specific antigen have led to earlier diagnosis and, presumably, to more effective management. This article reviews the current pharmacological treatment options in the management of prostate cancer.

INTRODUCTION
According to American Cancer Society statistics in 2002, prostate cancer is the most common cause of cancer in men, with an estimated 189,000 new cases identified each year. It is the second leading cause of cancer death in men, following lung cancer. Relative survival after a diagnosis of prostate cancer has improved over the years, and currently the estimated 10-year survival rate is 75%. The earlier the cancer is detected, the more favorable the survival rate; the 5-year survival rate in patients whose prostate cancer is discovered early, while it is still in the local and regional state, is 100%. A

SCREENING
Regular screening with the prostate-specific antigen (PSA) test and the digital rectal examination (DRE) can result in early detection and treatment. Normal PSA levels range from 0 to 4 ng/ml. The use of PSA as a screening test is highly controversial because of the relatively high prevalence of prostate cancer at autopsy compared to the relatively low mortality rate from the disease. PSA values can be elevated not only due to prostate carcinoma but also by benign prostatic hyperplasia (BPH), prostatitis, recent ejaculation, or recent biopsy. Despite the possibility of false-positive results, both the American Cancer Society and the American Urological Society recommend that the PSA, along with a DRE, be offered annually to men ages 50 and older with a life expectancy of at least another 10 years. These screenings are recommended earlier in men of African-American descent, who have a 50% higher risk of developing the disease, and in individuals with a family history of the disorder. The probability of prostate cancer also increases with age, from one in 48 for men ages 40 to 59 to one in eight for men ages 60 to 79.

Early signs and symptoms can also serve as an indicator to recommend screening, but localized disease is commonly asymptomatic. Symptoms may include weak or interrupted urine flow, inability to urinate, difficulty controlling urine flow, urinary frequency, nocturia, hematuria, and dysuria.

STAGING
Most diagnoses of prostate cancer are made following an abnormal PSA result and transrectal ultrasonography (TRUS). The pathological stage can be assessed after the surgical removal and examination of the prostate gland, seminal vesicles, and local lymph nodes. The tumor-node-metastasis (TNM) staging classification system includes categories for prostate cancer with no palpable abnormality (T1), palpable tumor but confined to the prostate gland (T2), and cancer that has extended outside the gland (T3 and T4). Nodal (N) involvement and distant metastases (M) are also incorporated into the staging system. Other systems for staging have also been developed combining information from the DRE, biopsy, a PSA test, TRUS, and a Gleason score (histological grade). Staging and treatment of localized disease are also discussed by Roth. These systems are used to direct treatment and to assess the probability of cure.

TREATMENT
Prostate cancer treatment is dependent on patient age, staging, and comorbid conditions. The American Cancer Society and the National Comprehensive Cancer Network (NCCN) have developed guidelines for the treatment of prostate cancer based on risk for recurrence and expected survival. In the earliest stages of clinically localized prostate cancer (T1-2, N0, M0) or in patients with a life expectancy of less than 10 years from the time of diagnosis, conservative management or “watchful waiting” without active treatment, localized therapy, or combined systemic and local therapy might be appropriate.

Surgery and Radiotherapy
For patients with disease confined to the prostate gland, the most common treatment option is surgery along with a radical perineal prostatectomy or prostato seminalovesiculectomy, including removal of all prostatic tissue. In a recent randomized trial conducted by the Scandinavian Prostatic Cancer Group, men with localized prostate cancer who underwent a radical prostatectomy, compared with watchful waiting, experienced a reduction in prostate cancer–specific mortality (4.6% versus 8.9%, P = .02) and a decrease in frequency of distant metastases (10.1% versus 15.5%, P = .03). No difference was found between the groups in overall mortality. In addition, men who underwent

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surgery had a higher incidence of erectile dysfunction and urinary incontinence; however, nerve-sparing surgery was not routinely performed in this trial. The external validity of this trial is unclear because the study population primarily included men who had palpable disease, with a diagnosis established in only 10% of cases as a result of elevated PSA levels.

External beam radiotherapy is another option for men with localized disease and can be an alternative to surgery in men with a comorbid condition, such as cardiovascular disease. For men with small tumors confined to the prostate gland (stage T1 or T2), brachytherapy, the interstitial implantation of radioactive seeds directly into prostatic tissue is a one-time treatment alternative to external beam radiotherapy.

Complications of surgery, radiation, and brachytherapy can include urinary incontinence, impotence, and rectal bleeding, all of which may limit the usefulness of these treatments. Newer irradiation techniques and nerve-sparing surgical techniques can decrease the incidence of treatment-related adverse effects. Postoperatively, erectile dysfunction can be treated with sildenafil citrate (Viagra®, Pfizer), the intraoperative use of cavernous nerve stimulation, and grafting of peripheral nerves to restore innervation of the corpora cavernosa.

Hormone Therapy
Prostate cancer cell growth is hormone-dependent and can become hormone-independent later in the course of the disease. In metastatic disease, bilateral orchiectomy (surgical removal of the testes) is the preferred method of treatment because of the complete blockade of androgens; however, as a result of the psychological trauma associated with this method, many patients consider this procedure unacceptable.

Hormonal therapy can decrease androgen production and is considered when initial curative therapy with radical prostatectomy or radiation therapy has failed or when the cancer is advanced. Hormonal therapy is not curative but can provide prolonged remission by shrinking tumor size and by decreasing symptoms such as pain and incontinence.

Pharmacological treatment options consist of agents that lower serum testosterone levels and agents that interfere locally with the binding of testosterone and dihydrotestosterone to the androgen receptor (Figure 1).

Luteinizing Hormone–Releasing Hormone Analogues
Luteinizing hormone-releasing hormone (LHRH) analogues, or LHRH agonists, include goserelin acetate and leuprolide acetate. These agents bring about a biphasic response by initially increasing luteinizing hormone (LH) and follicle-stimulating hormone (FSH), followed by down-regulation of the release of gonadotropic hormone–releasing hormone (GnRH) in the hypothalamus and gonadotropins in the anterior pituitary gland. This down-regulation reduces androgen synthesis in the testes, causing a chemical castration. The initial rise in testosterone may result in a clinical flare of the disease with a transient increase in tumor growth and an increase in other symptoms, such as urinary obstruction and bone pain in men with metastatic disease.

Goserelin (Zoladex®, AstraZeneca) is available as a monthly and as a 3-month implant that is administered subcutaneously. A clinical trial of 401 patients with localized advanced prostate cancer compared irradiation alone versus goserelin plus irradiation. The results showed a five-year survival rate of 79% in the combined treatment group and 62% in the irradiation-only group (95% confidence interval [CI]: 72–86 and 52–72, \( P = .001 \)).

Leuprolide acetate is available as an injectable suspension (Eli-gard®, Atrix Laboratories), given subcutaneously monthly or every 3 three months; as a long-acting depot formulation (Lupron Depot®, TAP Holdings), given intramuscularly, also monthly or every three months; or as a subcutaneous implant (Viadur®, Alza Corporation), given every 12 months.

The efficacy of goserelin and leuprolide appears similar, but a large-scale comparative trial has not been conducted. Another LHRH analogue, triptorelin (Trelstar®, Debiopharm Recherche), has a twofold greater potency than leuprolide and was approved for use in prostate cancer in 2000. In a randomized trial, triptorelin suppressed testosterone to castration levels in 91% of patients with advanced prostate cancer during the first month of treatment, with levels maintained through day 253 in 96% of patients.

The individual selection of an LHRH analogue depends on cost and on the desired administration schedule. Whether any possible differences in morbidity and mortality exist has not yet been established. Timing of hormonal therapy for prostate cancer has been a point of controversy in the literature. Early treatment with hormonal therapy can be expensive and can cause a rise in anxiety as a result of frequent follow-up testing with PSA tests and an increased incidence of adverse effects caused by long-term use. All of the LHRH analogues can cause hot flushes, decreased libido, impotence, gynecomastia, fluid retention, anemia, fatigue, cognitive impairment, and bone demineralization, sequelae that affect a patient’s quality of life. Using hormonal therapy intermittently may decrease some of these acute toxicities. Mounting evidence supports initiating treatment once the disease is locally advanced or once recurrent or metastatic disease is diagnosed.

In a follow-up phase III trial of the previously mentioned study of patients with locally advanced disease, it was shown that patients randomly assigned to radiation therapy plus three years of adjuvant hormonal therapy with goserelin had a significantly better five-year survival over patients receiving radiation therapy initially plus hormonal therapy only at disease recurrence. The five-year clinical disease-free survival rates were 74% (95% CI: 67–81) in the combined treatment group and 40% (95% CI: 32–48) in radiation alone.

Because hormone suppression causes systemic castration, long-term therapy with LHRH analogues can result in a severe decline in bone density. Prevention of osteoporosis in these patients is imperative in order to decrease fracture risk. Bisphosphonates, such as pamidronate (Aredia®, Novartis) and zoledronic acid (Zometa®, Novartis), have been evaluated in protecting the bone mineral density during treatment with LHRH analogues. It has been suggested that bisphosphonates not only might protect bone density but also might have antitumoral and antimetastatic potential.

Abarelix, an agent similar to an LHRH analogue, is currently under review by the U.S. Food and Drug Administration (FDA). Abarelix is a modified GnRH antagonist and offers an advantage over LHRH agonists through its direct antagonist action, which avoids the initial flare phenomenon. This agent has not yet un-
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GnRH antagonists have undergone long-term studies, and clinical data are too limited to assess its role in therapy. It is possible that GnRH antagonists might be an alternative treatment option to LHRH agonists in prostate cancer if their efficacy proves similar and if the reduced adverse effects linked to the testosterone surge can be confirmed.

Antiandrogens

Because androgens are also produced outside the testes in the adrenal glands, antiandrogens such as **bicalutamide** (Casodex®, AstraZeneca), **flutamide** (Eulexin®, Schering-Plough), and **nilutamide** (Nilandron®, GH Besselaar Associates) are used to block the action of testosterone at the cellular level. In contrast to the injectable LHRH analogues, these agents are given orally one to three times per day. Because monotherapy with an antiandrogen can induce a compensatory rise in LH release from the pituitary gland and a subsequent rise in testosterone levels, combination therapy with an LHRH analogue is usually recommended.

To provide adequate androgen deprivation, physicians commonly use the combination therapy of an antiandrogen with an LHRH analogue, orchietomy, or radiotherapy. This combination may be referred to as "chemical castration," "maximal androgen deprivation," or "combined androgen blockade." The antiandrogens can also be used to block the flare response from the initial rise in testosterone from LHRH analogues.

Toxicities differ among the agents, but all include gynecomastia, fatigue, elevation in serum transaminases, and diarrhea (Table 1). Flutamide is more frequently associated with diarrhea and gynecomastia and, rarely, with liver toxicity. Bicalutamide and nilutamide offer an advantage over flutamide because they can be given as a once-daily formulation, whereas flutamide administration is required three times daily. Nilutamide is associated with visual impairment, causing a decrease in adaptation to darkness and interstitial pneumonitis. It is recommended that visual examinations be conducted periodically and that a chest radiograph be obtained before initiation of nilutamide and then repeated periodically. These unique adverse effects have not been reported with bicalutamide.

Controversy exists as to whether a combined regimen that in-

### Table 1 Pharmacological Treatment Options for Prostate Cancer

<table>
<thead>
<tr>
<th>Generic/Brand Name</th>
<th>Dosage/Frequency</th>
<th>Side Effects/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LHRH Analogues</strong></td>
<td></td>
<td></td>
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<tr>
<td>Leuprolide (Lupron Depot®, TAP Holdings)</td>
<td>7.5 mg IM q mo</td>
<td>All: hot flushes, skeletal pain, impotence, gynecomastia, osteopenia</td>
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<tr>
<td></td>
<td>22.5 mg IM q 3 mo</td>
<td>Keep vials refrigerated; fractional dose is not equivalent to monthly formulation</td>
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<tr>
<td></td>
<td>30 mg IM q 4 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 mg SQ q.d.</td>
<td></td>
</tr>
<tr>
<td>Goserelin (Zoladex®, AstraZeneca)</td>
<td>3.6 mg SQ q 28 days</td>
<td>Implant system</td>
</tr>
<tr>
<td></td>
<td>10.8 mg SQ q 3 mo</td>
<td></td>
</tr>
<tr>
<td>Triptorelin (Trelstar®, Debio Recherche)</td>
<td>3.75 mg IM q mo</td>
<td>Monitor BP for first 4–8 wk</td>
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<tr>
<td><strong>Antiandrogens</strong></td>
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<td></td>
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<tr>
<td>Bicalutamide (Casodex®, AstraZeneca)</td>
<td>50 mg PO q.d.</td>
<td>All: hot flushes, fatigue, increase in liver function tests, gynecomastia</td>
</tr>
<tr>
<td>Flutamide (Eulexin®, Schering-Plough)</td>
<td>250 mg PO q 8 hr</td>
<td>Long terminal half-life</td>
</tr>
<tr>
<td>Nilutamide (Nilandron®, GH Besselaar Associates)</td>
<td>300 mg PO q.d.</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td><strong>Other Hormonal Agents</strong></td>
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<td></td>
</tr>
<tr>
<td>Megestrol Acetate (Megace®, Bristol-Myers Squibb)</td>
<td>80–160 mg/day</td>
<td>Edema, increased appetite, myelosuppression</td>
</tr>
<tr>
<td>Aminoglutethimide (Cytadren®, Novartis)</td>
<td>125 mg PO q.i.d</td>
<td>Sedation, skin rash, weakness</td>
</tr>
<tr>
<td>Ketoconazole (Nizoral®, Janssen)</td>
<td>600–1200 mg/day</td>
<td>GI upset, hepatotoxicity</td>
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<tr>
<td>Medroxyprogesterone (Provera®, Pharmacia &amp; Upjohn)</td>
<td>1 g IM 3x/wk x 5 wk, then 1 g IM weekly</td>
<td>Gynecomastia, loss of libido, venous thrombosis</td>
</tr>
</tbody>
</table>

BP, blood pressure; g, gram; GI, gastrointestinal; IM, intramuscularly; LHRH, luteinizing hormone-releasing hormone; PO, by mouth; q.d., every day; q.i.d., four times a day; SQ, subcutaneously.
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Incluced androgen blockade with LHRH analogues and an antiandrogen is superior to chemical castration without an antiandrogen. Randomized trials have reported both positive and negative results, with the majority showing no difference.

The National Cancer Institute sponsored a randomized trial of 603 men with previously untreated metastatic disease. It was found that the combination of leuprolide plus flutamide versus leuprolide plus placebo resulted in a longer progression-free survival (16.5 vs. 13.9 months; \( P = .039 \)) and a longer median overall survival than treatment with leuprolide plus placebo (35.6 vs. 28.3 months; \( P = .035 \)). Other studies, including a meta-analysis of 27 randomized trials involving maximum androgen blockade using flutamide, nilutamide, or cyproterone acetate, did not show this survival advantage for combined androgen blockade. Cyproterone acetate has progestational properties that may be used symptomatically for the management of BPH. It works by its potential for pain flare, thrombosis, hypertension, and hyperglycemia.

Although diethylstilbestrol (DES), a semisynthetic estrogen analogue, had been used frequently in the past to decrease testosterone levels, its use is limited because of its significant cardiovascular complications, including edema, congestive heart failure, myocardial infarction, cerebrovascular accidents, phlebitis, and pulmonary embolism. Similar survival rates and quality-of-life benefits have been demonstrated by LHRH analogues without the excess cardiovascular mortality. Aminoglutethimide (Cytadren®, Novartis) is also a rarely used second-line hormonal agent that inhibits the synthesis of androgens, glucocorticoids, and mineralocorticoids. Therapy is usually initiated with 250 mg twice daily and gradually increased to four times a day based on tolerance. Given the prevention of synthesis of all adrenally derived steroids, concurrent replacement of glucocorticoids is necessary.

High-dose ketoconazole (Nizoral®, Janssen), an antifungal agent (400 mg three times a day), can also produce a rapid chemical castration through inhibition of adrenal steroid synthesis. Because ketoconazole requires an acidic environment for absorption, it is usually given with citrus juices; coadministration with antacids, histamine (\( H_2 \)) antagonists, and proton pump inhibitors should be avoided. Long-term use is limited by hepatotoxicity.

Finasteride (Proscar®, Merck), a 5α-reductase inhibitor, can be used symptomatically for the management of BPH. It works by blocking the conversion of testosterone to dihydrotestosterone. It has been demonstrated to have minimal effects on PSA levels but continues to have a limited role in the treatment of prostate cancer. Clinically, it has been incorporated as part of an intermittent androgen blockade regimen during the “off” period. This treatment approach has not been compared with more established regimens, and mortality data are unknown.

The role of finasteride in the prevention of prostate cancer is being evaluated in the ongoing Prostate Cancer Prevention Trial (PCPT), a randomized, double-blinded, placebo-controlled study.
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sponsored by the National Cancer Institute. This trial represents a shift from secondary prevention efforts, such as early detection and treatment of prostate cancer, to primary prevention.24

Chemotherapy

Chemotherapy may be considered in patients who have hormone-refractory or androgen-independent prostate cancer; however, no current treatment regimen has been shown to improve survival in a prospective, randomized clinical trial.25 Chemotherapy can be used to delay progression, and it can palliate symptoms of the disease, including pain. Single agents have shown relatively low response rates. One small trial of 25 patients with endocrine-refractory prostate cancer receiving weekly infusions of doxorubicin (Adriamycin®, Pharmacia) showed an overall response rate of 84%.26 The NCCN Practice Guidelines also recognize combinations of ketoconazole and doxorubicin, mitoxantrone and prednisone, and estramustine combined with one of the following: vinblastine, etoposide, paclitaxel, or docetaxel.5 One combination that has been shown to improve pain and quality of life is mitoxantrone with prednisone.27

Mitoxantrone (Novantrone®, Wyeth), an anthracyclinedione similar to doxorubicin, inhibits topo-isomerase II, the enzyme responsible for DNA helix supercoiling, thus resulting in decreased replication. When mitoxantrone was combined with prednisone in men with metastatic disease, it was fairly well tolerated and effective in achieving a “palliative response,” or a significant reduction in pain when compared to prednisone alone.27

Estramustine (Emcyt®, Pharmacia and Upjohn), a synthetic combination of estrogen and nitrogen mustard, affects microtubule assembly and disassembly and thus prevents cell division. After undergoing extensive first-pass metabolism, it is converted to an estrone analogue that exerts an antigonadotropin effect. Its adverse effects include fatigue, nausea, vomiting, edema, and venous thromboembolism. Estramustine is both an oral and a recent intravenous treatment option in patients whose hormone therapy has failed, and it can also be used in combination with other agents, including taxanes and etoposide.28 Randomized trials are currently under way to evaluate other chemotherapeutic regimens and, it is hoped, to address the question of whether this agent should be used earlier in the course of the disease.

Dietary Supplements

Dietary supplements, such as saw palmetto, soy, citrus pectin, and PC-SPES, have also been touted for use in the treatment of prostate cancer. PC-SPES is a combination of eight herbs and phytoestrogens, including chrysanthenum, reishi mushroom, licorice, sanchi ginseng, and saw palmetto. Its action is similar to that of DES, and therefore it is contraindicated in patients with a history of thromboembolic or significant cardiovascular disease because of the risk of thromboembolic side effects. The FDA recently warned consumers to stop using PC-SPES because the California Department of Health Services found it to be adulterated with traces of prescription medications, including DES, alprazolam, and warfarin.29 The manufacturer has since voluntarily recalled this product.

Saw palmetto is a dietary supplement similar in action to the 5α-reductase inhibitor finasteride. It can falsely lower the PSA value, which may rebound to its true level once it has been discontinued. Saw palmetto is not recommended for the treatment of prostate cancer.30 As with all dietary supplements, caution must be used until quality standards for formulations are in place.

A number of studies have questioned the possibility of preventing prostate cancer. In a study sponsored by the National Cancer Institute, healthy men aged 55 and older are being recruited to test whether selenium and vitamin E can reduce the incidence of prostate cancer.31 This trial is based on evidence that these antioxidants play a role in the prevention of head and neck cancer. Final results are anticipated in 2013.

CONCLUSION

Until treatment options are clearly identified to significantly affect survival, the treatment of prostate cancer will continue to focus on improving quality of life. Although hormonal therapy is effective in controlling localized disease, the expense and adverse effects limit its use.

The treatment options for prostate cancer are quite expensive. Even though the lifetime cost of an antiandrogen or an LHRH analogue is substantially higher than the one-time cost of orchectomy, some patients might not consider this surgical procedure acceptable. Improvement in the prostatectomy surgical technique, particularly for the retropubic procedure, can protect the neurovascular supply to the corpora cavernosa and therefore preserve potency in most patients younger than age 60 without compromising the completeness of the operation.

At this time, the optimal regimen and timing of administration of hormonal agents in the treatment of prostate cancer are still a matter of debate. Trials comparing combined androgen blockade regimens with monotherapy, followed by institution of a combined regimen at the time of recurrence, have not been completed. Treatment remains patient-specific and should be based on the extent of tumor, PSA level, Gleason score, quality of life, and life expectancy. Future agents being studied for the treatment of prostate cancer include angiogenesis inhibitors, signaling inhibitors, vaccines, and oncolytic viruses, all of which offer some promise.

REFERENCES


