Feature Article

Palliative Care Options for Advanced Prostate Cancer

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ABSTRACT

What are the main symptoms experienced by patients with advanced prostate cancer, and how should they be managed? Due to increased longevity and disease awareness, the reported incidence of prostate cancer is rising. Although patients who present with early, localized disease can be offered curative treatment, patients presenting with locally advanced or metastatic disease currently receive only palliative treatment. Due to the hormone-dependency of prostate cells, androgen ablation has proved successful in delaying the progression of advanced disease. Luteinizing hormone-releasing hormone (LHRH) agonists, LHRH antagonists, and estrogens are all effective agents for medical castration. Antiandrogens can also be used to block the effect of testosterone at target prostate cells. The main side effects of surgical/medical castration are reduced bone mineral density and impaired sexual function, reflecting the physiologic role of testosterone metabolites. Progression of advanced disease following androgen ablation is inevitable due to the development of hormone-independent neoplastic prostate cells. At this stage, the withdrawal of antiandrogen treatment can be effective, producing a second response and a concomitant fall in prostate-specific antigen levels. Other options to treat progressive disease include adrenal suppression and modern chemotherapy agents. In addition to treatment-related side effects, patients with prostate cancer often experience ureteric obstruction and hematuria, due to the enlarged prostate gland. Resulting bone metastases can cause further complications, including spinal cord compression, pathologic fractures, pain, and anemia. The plethora of symptoms experienced by patients with advanced prostate cancer highlight the need for a multidisciplinary team to ensure that effective palliative treatment is given.

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INTRODUCTION

Prostate cancer is the second most common cancer death in men in the developed world.[1] With increasing longevity and awareness of it, the reported incidence of prostate cancer is rising.[2] Increasingly, patients are presenting with early prostate cancer, namely pathologic stages T1 and T2, for which treatment with curative intent can be offered, ie, surgical radical prostatectomy or radiotherapy (brachytherapy or external beam radiotherapy).[3]

For patients who present with locally advanced (T4) or metastatic (M1) disease, support for watchful-waiting policies, or deferred treatment, is waning in light of evidence of the value of immediate hormone manipulation treatment.[4] Due to the androgen-dependence of prostate cancer cells, first shown by Huggins and Hodges in the early 1940s, androgen ablation has been established as the benchmark of treatment for patients with advanced disease.[5] However, due to the unpredictable but frequent development of hormone-independent neoplastic cells (Figure 1), androgen ablation is a well-recognized palliative option in the management of advanced prostate cancer.

This review discusses the palliative care of men with advanced prostate cancer, focusing on treatment, disease, and quality-of-life issues.

TREATMENT ISSUES

Metastatic cancer of the prostate can be treated by hormonal manipulation to prevent further spread. Current androgen ablation modalities include medical or surgical castration. Medical castration can be achieved using luteinizing hormone-releasing hormone (LHRH) agonists, LHRH antagonists, or estrogen derivatives, which abolish testosterone secretion by the gonads. Pure antiandrogens can also be used for medical castration. Rather than abolishing

TALKING POINTS Physicians Pharmacy Formulary Cancer Nurses

There is an increasing awareness of osteoporosis in prostate cancer patients following long-term luteinizing hormone releasing hormone (LHRH) therapy.

The choice of LHRH agonist for prostate cancer treatment may be guided by the associated side effect profiles of these agents.

Individualized patient care depends upon clear knowledge of treatment choices, including the available agents and their associated side effects.

A multidisciplinary team is essential to providing support and palliative care in patients with metastatic prostate cancer.

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testicular hormone secretion, antiandrogens block the effects of testosterone on target cells. The different modes of action of the various therapies reflect the different hormonal control pathways of the prostate, as shown in Figure 2.

The choice of androgen ablation therapy should be made by both the patient and treating physician, following detailed discussions regarding the likely adverse effects of each option. The adverse effects of testosterone ablation primarily result from loss of the physiologic effects of testosterone (Figure 3). While all hormone manipulation therapies result in the loss of some of these physiologic effects, pure antiandrogens could, arguably, be seen as preserving the effects of direct testosterone action, as they block only those attributed to 5-dihydrotestosterone (Figure 3).

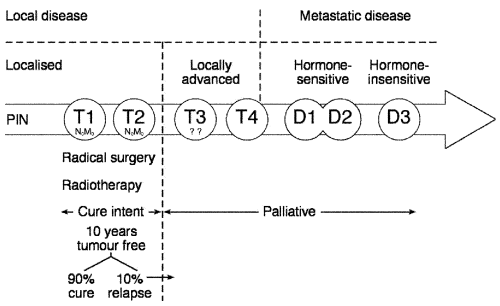
The two principal adverse effects of androgen ablation are reduced bone mineral density (BMD) and reduced sexual function. Recent reports have highlighted the issue of osteoporosis in men receiving LHRH agonist therapy. In 1997, Townsend et al reported a 9% fracture incidence in patients treated with LHRH agonists, of which 5% were osteoporotic fractures.[6] Suzuki et al found decreased BMD in patients who had been receiving LHRH agonist therapy for more than 12 months.[7] Because of these reports, periodic BMD and bone marker tests are now recommended in patients treated with LHRH agonists. Data from Diamond et al indicate a role for adjuvant therapy (intermittent cyclic etidronate disodium) to prevent high bone metabolic turnover and decrease the risk of fractures in these patients.[8]

Preliminary data presented by Iverson et al[9] suggest that treatment with bicalutamide, a nonsteroidal antiandrogen, may provide an alternative to castration in patients with prostate cancer for whom hormone therapy is indicated. Patients receiving long-term bicalutamide have BMD values similar to those found in the general, age-matched population, whereas castrated patients are likely to be at an increased risk of fractures, due to reduced BMD (Tyrrell CJ, et al, personal communication, 2000). However, bicalutamide therapy is inferior to orchiectomy in the management of advanced prostate cancer, where a difference in survival of 42 days in favor of orchiectomy has been observed.[9]

Impaired sexual function, as a direct effect of castrate androgen ablation, is an inevitable outcome in patients treated by orchiectomy. Several studies have shown that pure antiandrogen monotherapy-treated patients maintain sexual function and libido, which is of enormous value to their quality of life.[10-13]

Additional adverse effects of androgen ablation are associated with individual therapies. The clinical value of estrogens has been controversial in view of associated cardiovascular complications, particularly thromboembolic phenomenon, hypertensive crisis, and salt and water retention.[14] The initial rise in serum testosterone and resulting flare following initiation of therapy with LHRH agonists is avoided by using LHRH antagonists. Patients treated with pure nonsteroidal antiandrogens do not appear to experience any associated thromboembolism or fluid

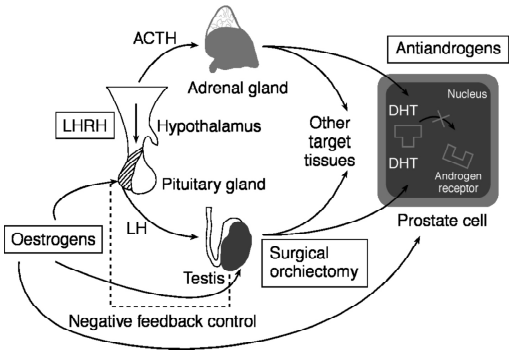
FIGURE 1. PROGRESSION PATHWAY OF PROSTATE CANCER



PIN=prostatic intraepithelial neoplasia.

Kaisary AV, Knight R. *Oncology Spectrums*. Vol 2. No 7. 2001.

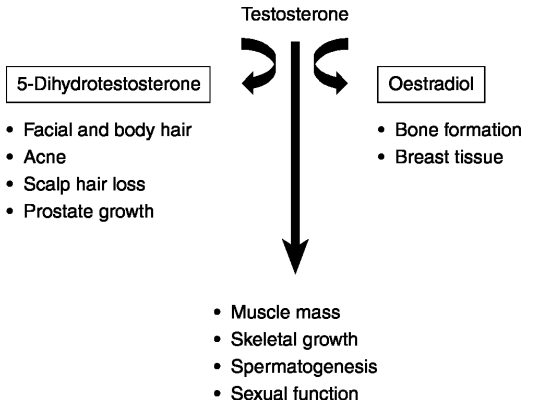
FIGURE 2. ENDOCRINOLOGIC CONTROL OF THE PROSTATE



ACTH=adrenocorticotropic hormone; LHRH=luteinizing hormone-releasing hormone; LH=luteinizing hormone; DHT=dihydrotestosterone.

Kaisary AV, Knight R. *Oncology Spectrums*. Vol 2. No 7. 2001.

FIGURE 3. EFFECTS OF TESTOSTERONE AND ITS METABOLITES IN MEN



Kaisary AV, Knight R. *Oncology Spectrums*. Vol 2. No 7. 2001.

retention. Nilutamide, however, is associated with a notable incidence of decreased ability to adapt to dark, nausea, alcohol intolerance, and occasional interstitial pneumonia.[15] Flutamide is associated with gastrointestinal tract intolerance, particularly diarrhea, which can result in cessation of therapy.[16] Quality-of-life data from patients treated for 12 months with bicalutamide suggested significant benefits in sexual interest and physical activity.[9] In addition, the long half-life of bicalutamide allows once-daily dosing, providing a more convenient regimen for patients.[17]

Due to the frequent development of hormone-independent neoplastic cells, androgen ablation is only a palliative treatment for advanced prostate cancer, with disease progression inevitable. The average duration of progression-free survival in patients with advanced prostate cancer treated with primary androgen ablation therapy is approximately 18–24 months. The subsequent development of hormone-independent neoplastic cells, although poorly understood, is thought to be associated with increasing genetic instability.[18]

Autonomous cancer cells may result from genetic mutations, which cause overexpression of genes associated with growth stimulation (oncogenes) or growth suppression (tumor suppressor genes). The role of growth factors in the regulation of hormone-dependent prostate cells is illustrated in Figure 4. Testosterone induces the release of growth factors and transcription agents from stromal cells. These factors travel to neighboring cells to exert their effects. This paracrine activity is seen in both benign and malignant prostate cells. Prostate cells also produce growth factors that attach to receptors on the surface of the same cell, stimulating growth. This autocrine effect occurs in malignant cells only. Furthermore, growth factors and transcription agents can be produced and act within an individual cell, known as intracrine activity. The paracrine, autocrine, and intracrine modes of action of growth factors are thought to play a major role in the development of androgen independence.

Laboratory and clinical data have shown that antiandrogen withdrawal may be a useful strategy in the treatment of patients with locally advanced and metastatic prostate cancer who have evidence of disease progression despite androgen blockade. This second-response phenomenon, concurrent with antiandrogen withdrawal, has been reported in patients treated with both flutamide and bicalutamide.[19] The associated fall in levels of prostate-specific antigen (PSA) following cessation of treatment occurs later in bicalutamide-treated patients than in those treated with flutamide, possibly due to differences in the pharmacologic half-life of the two drugs. The use of PSA levels as an indicator of response, while controversial, is widely accepted.

Several other treatments are available to patients with progressive disease who fail to show a second response to antiandrogen withdrawal. The effect of discontinuing antiandrogen therapy is enhanced by adrenal suppression, with such agents as ketoconazole, corticosteroids, aminoglutathamide, and liarazole. Agents that act via other cellular receptors include tamoxifen, somatostatin analogues, calcitriol, retinoids, and endothelin suppressors/antagonists. The impact of the specific adverse effects associated with each of these agents on the patient's quality of life needs to be considered when prescribing treatment.

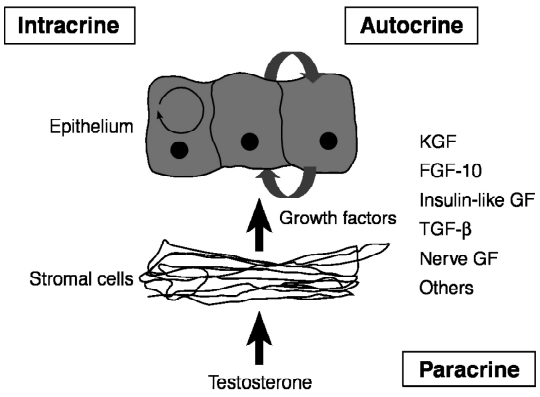
Recent trials have demonstrated the benefits of modern chemotherapy in androgen-independent prostate cancer. The most effective cytotoxic therapies at the present time are combinations of estramustine phosphate with taxanes and etoposide. Regimens combining ketoconazole with estramustine, vinblastine, or bisphosphonates and mitoxantrone combined with hydrocortisone seem to be worthy of further evaluation.[20]

DISEASE ISSUES

Prostate cancer often leads to a range of medical problems that can be attributed to changes in the gland itself or to development of associated metastases. An enlarged prostate gland can obstruct the bladder outlet, leading to troublesome urinary symptoms that may be present at diagnosis, may develop in a patient who is being managed by a watchful-waiting policy following diagnosis, or may occur during active treatment. Perurethral prostatectomy, hyperthermia,[21,22] laser ablation,[23] cryotherapy,[24] prostate stent insertion,[25] and high-intensity-focused ultrasound therapy[26] are modalities that can be used to achieve satisfactory symptomatic relief.

Ureteric obstruction may result from either direct extension of the prostatic tumor into the bladder base and distal ureters or from ureteric compression by massive pelvic lymph node involvement. Ureteric obstruction is an uncommon, late event, rarely presenting suddenly, with signs and symptoms of acute renal failure. In patients who are not receiving any form of androgen-deprivation therapy, urgent intervention can be warranted, depending on the patient's clinical condition. Treatment with LHRH agonists is contraindicated in an impending or existing ureteric obstruction in a newly diagnosed case of prostate cancer. The

FIGURE 4. ANDROGENS AND GROWTH FACTORS



KGF=keratinocyte growth factor; FGF=fibroblast growth factor; GF=growth factor; TGF-β=transforming growth factor-beta.

Kaisary AV, Knight R. *Oncology Spectrums*. Vol 2. No 7. 2001.

simplest and most effective intervention to achieve androgen withdrawal in such a case is surgical orchiectomy, performed under local anesthetic or sedation. Endoscopic retrograde or percutaneous antegrade placement of ureteral catheters or stents allows urinary drainage of the kidneys. Modern imaging techniques allow accurate placement and easy change of these stents every 10–12 weeks or at longer intervals.

Hematuria is not an uncommon event, and it can be combated by medical therapy, eg, vitamin K and tranexamic acid, and blood transfusion as necessary. At times, endoscopic diathermy or resection of prostatic tissue is necessary to halt the bleeding.

Bone metastases, which arise via hematologic spread of neoplastic prostate cells to the bone marrow, result in osteolysis as the tumor grows within the bone marrow. Osteoblastic activity also occurs as the bone attempts to heal and remodel. These changes occur at the sites of red bone marrow, usually confined to the axial skeleton and proximal long bones (femora and humeri). Common clinical complications include spinal cord compression, pathologic fractures, pain, and anemia.

Magnetic resonance imaging (MRI) is the preferred imaging option to evaluate spinal cord compression, which is a clinical emergency.[27] However, examination of the entire spinal column may not be feasible, as it is a lengthy procedure. If used, MRI may be limited to the suspected region, particularly in patients who are unable to cooperate with the examination. In acute presentation in patients not previously treated with androgen ablation, immediate surgical orchiectomy in combination with corticosteroid therapy may provide dramatic relief. Irradiation of the affected area can be of value in achieving pain control.

Pathologic fractures of long bones are optimally managed by internal fixation, which stabilizes the bone, helping to maintain skeletal integrity and to reduce further pain.[28] Postoperative radiation therapy can further aid in pain control and halt the progress of metastatic lesions, which could eventually lead to loosening of the fixation prosthesis. Other measures to alleviate pain include nonsteroidal anti-inflammatory agents, opioids, bisphosphonates, radioisotopes, and chemotherapy.[29-32]

Soft tissue metastatic disease in prostate cancer is not uncommon. At some sites, it can also lead to persistent symptoms, eg, chronic cough in metastatic pulmonary disease, and should be managed symptomatically if warranted, in addition to systemic disease control.

QUALITY OF LIFE

Patients with terminal prostate cancer are managed primarily with palliative care. A multidisciplinary team approach is best to treat the plethora of symptoms these patients experience. Continual support from both the hospital and the community is required to ensure that the patient experiences the best quality of life possible, both physically and emotionally. Communication between patients and their caregivers is vital to anticipate and prevent additional complications. **OS**

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