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The evolving role of hormone therapy in advanced prostate cancer

ABSTRACT

Earlier diagnosis and treatment of prostate cancer has changed the face of late-stage disease, and the use of mainstay hormonal therapies—orchiectomy, luteinizing hormone releasing-hormone analogs, and combined androgen ablation—are evolving rapidly. New approaches such as antiandrogen monotherapy and intermittent therapy are being evaluated. In addition, palliative treatments for patients with androgen-independent tumors have expanded.

KEY POINTS

The most common clinical presentation of advanced prostate cancer is a rising prostate-specific antigen level following primary therapy (radical prostatectomy or radiotherapy or both).

Due to the negative psychological implications of orchiectomy, many patients are opting for treatment with luteinizing hormone-releasing hormone analogs.

Because studies of combined androgen ablation have not provided conclusive results, it is reasonable to forego antiandrogen therapy for patients who undergo bilateral orchiectomy.

Management options for patients with androgen-independent prostate cancer are expanding and include antiandrogen removal, antiandrogen therapy, and glucocorticoids.

OUR UNDERSTANDING AND APPROACH to the management of advanced prostate cancer have changed rapidly in the past few years. This article discusses the evolving clinical presentation of advanced disease and hormonal therapy options that are used palliatively to manage it, as well as how to address an emerging therapeutic dilemma—patients with a rising prostate-specific antigen (PSA) level following hormonal therapy. It also covers the newest treatments for hot flushes, the main adverse effect of therapy.

PATIENTS USUALLY HAVE RECEIVED PRIMARY TREATMENT

The historical image of metastatic prostate cancer was that of a newly diagnosed patient with diffuse bone pain, weight loss, and a rock-hard prostate. Now that PSA screening is increasing, prostate cancer is being diagnosed and treated earlier. Thus, the typical presentation of a patient with advanced disease today is one with a rising PSA level following primary therapy (radical prostatectomy or radiotherapy or both). After radical prostatectomy, the PSA level should decline to undetectable levels. A postoperative rise indicates that residual or recurrent tumor is present.

Patients treated with radiotherapy alone present a more complicated picture, given the presence of a residual prostate gland. However, a postradiation PSA nadir of 0.5–1.0 ng/mL or less suggests a good prognosis. Although the natural history in patients with detectable PSA values following therapy remains poorly defined, emerging evidence suggests that some patients will do well for many years.[1] During that time, many will receive hormonal therapy.

FIRST-LINE THERAPY: ANDROGEN ABLATION

In advanced prostate cancer, the goal is to lower testosterone levels (which can temporarily shrink the tumor or slow its growth) with androgen ablation therapy. There are several options: bilateral orchiectomy, luteinizing hormone-releasing hormone (LHRH) analogs, and combination hormonal therapy.

Orchiectomy

Bilateral orchiectomy—the gold standard of treatment—causes testosterone levels to drop to castrate levels within hours. However, patients are increasingly opting for medical therapy with LHRH analogs instead, partly because of the negative psychological implications of surgical castration. Bilateral orchiectomy remains the treatment of choice for patients with spinal cord compression or diffuse, painful bone metastases. Adverse effects include reduced libido and hot flushes.

LHRH analogs

LHRH analogs have become the de facto standard of care for men with metastatic prostate cancer. Two LHRH analogs are available in the United States: leuprolide (Lupron) and goserelin (Zoladex). They are given as subcutaneous or intramuscular depot injections every 3 to 4 months, and are therapeutically equivalent to bilateral orchiectomy. Both drugs may initially cause testosterone levels to surge (testosterone flare) in 5% to 10% of men. Castrate levels of testosterone are typically obtained in 14 to 21 days.[2] Adverse effects include hot flushes, gynecomastia, loss of libido, fatigue, weight gain, lassitude, loss of muscle mass, and emotional lability.

LHRH analogs may also cause bone demineralization. The capability of LHRH analogs to cause osteoporosis is increasingly being recognized as patients are receiving hormonal therapy earlier in their disease course and are therefore exposed to these agents for protracted periods of time.[3]

A second generation of LHRH analogs is currently undergoing clinical trials. These newer agents, which include both LHRH agonists and true LHRH antagonists, may decrease the incidence of testosterone flares, shorten the time to achieve castrate testosterone levels, and increase the duration of effect to 6 months.

Combination therapy with nonsteroidal antiandrogens

In men, 5% to 10% of circulating testosterone comes from converted adrenal steroid precursors. Nonsteroidal antiandrogens, which act on the androgen receptor to inhibit the stimulatory effects of testosterone, are commonly given with either an LHRH analog or orchiectomy to block the effect of this remaining testosterone—a practice commonly referred to as combined androgen ablation.

Three agents are available in the United States: flutamide (Eulexin), bicalutamide (Casodex), and nilutamide (Nilandron). These are given as pills once or three times a day. Combination therapy causes a higher incidence of toxicity and costs significantly more than LHRH analog therapy or orchiectomy alone.

The role of combined androgen ablation was highlighted following the publication in 1989 of a major intergroup trial.[4] Patients with newly diagnosed metastatic prostate cancer were randomly assigned to receive either leuprolide and flutamide or leuprolide and placebo. Patients in the leuprolide-flutamide group survived a median of 35.6 months— 7 months more than the patients treated with leuprolide alone. The results of this study led to the widespread application of this therapeutic approach.

Bilateral orchiectomy is the gold standard of treatment

However, there was concern that patients in the leuprolide-placebo group might have experienced a testosterone flare that affected the outcome. This prompted a second major intergroup trial, in which all patients underwent orchiectomy to obviate the issue of testosterone flare and were randomized to receive flutamide or placebo. In this trial of 1,371 eligible patients, the results did not show a statistically significant difference in survival between the two groups.[5]

The role of combined androgen blockade in treating advanced disease remains controversial; more than 20 randomized trials and

two meta-analyses have reported divergent conclusions.[6] Based on our current knowledge, it is reasonable to manage patients who opt for orchiectomy without antiandrogen therapy.

Patients who choose combined androgen ablation should be counseled on the potential disadvantages (increased toxicity and cost) and benefit (possibly prolonged survival), and they should have significant input in the final decision.

SECOND-LINE THERAPIES

Even though first-line hormonal therapy produces very high response rates, nearly all patients ultimately develop progressive disease (clinically evident either as bone or lymph node metastases or a rising PSA in the absence of overt metastases) as a consequence of androgen-independent tumor growth. The management options for patients with androgen-independent prostate cancer are still somewhat limited but are expanding as our understanding of the disease process evolves.

Antiandrogen withdrawal

Antiandrogen withdrawal responses occur in 15% to 30% of patients

The initial therapeutic approach in a patient managed with combined androgen blockade is to withdraw the antiandrogen. This is based on an observation originally reported in the early 1990s by Kelly and Scher,[7] which they termed the flutamide withdrawal syndrome.

These investigators noted that a subset of patients treated with combined androgen blockade (orchiectomy or a gonadotropin-releasing hormone analog, plus flutamide) had declines in both PSA and visceral metastatic disease after flutamide was stopped following disease progression. Many other investigators have confirmed this observation and noted it to some degree with other antiandrogens and agents such as megestrol acetate and aminoglutethimide.

Withdrawal responses occur in 15% to 30% of patients, with a median duration of response of approximately 4 months. Although the mechanism of this phenomenon has not yet been identified, one theory suggests that mutations in the androgen receptor result in an altered response to antiandrogens and glucocorticoids.

Antiandrogen therapy

Flutamide, bicalutamide, and nilutamide have been used as second-line hormonal therapies in patients whose disease progressed after initial therapy. Responses (declines in PSA of more than 50%) occurred in 20% to 50% patients who were previously treated with castration alone.[8]

Although the commercially available antiandrogens are all chemically similar, there is some evidence of non-cross resistance: patients in two trials whose disease progressed despite initial therapy with flutamide responded to high-dose bicalutamide.

Despite these findings, no study has ever shown that second-line or later antiandrogen therapies lengthen patient survival. In addition, although these agents are typically well tolerated, they have drawbacks. The median duration of response is 3 to 4 months. Also, the out-of-pocket costs, which can range from $300 to $1,000/month, can be prohibitive for some patients.

Glucocorticoids

Glucocorticoids have long been recognized to benefit a subset of patients with symptomatic androgen-independent disease. In a recent clinical trial,[9] low-dose prednisone (7.5–10 mg/day) provided a palliative benefit for 21% to 40% of patients. The palliative benefit included a general improvement in quality of life, decreased pain, and a reduction in analgesic usage. Therapy is typically well tolerated, and the effects may last for several months.

LHRH analogs

In patients whose primary hormonal therapy was an LHRH analog, maintaining testosterone suppression by continuing LHRH therapy in the face of disease progression has become widely accepted. Although the literature is limited and conflicting, some evidence has shown that patients with androgen-independent disease have tumors with heterogeneous cell populations. A subset of these patients may still respond to testosterone withdrawal.

On the other hand, LHRH analogs play no role as second-line therapy in patients with disease progression who have previously undergone bilateral orchiectomy. Because

LHRH analogs are therapeutically equivalent to orchiectomy, they provide no additional benefit.

WHEN THE PATIENT IS ASYMPTOMATIC

Widespread PSA screening and case identification have resulted in earlier recognition of advanced disease. Thus, the number of patients with biologically defined androgen-independent prostate cancer (ie, rising PSA on hormone therapy with no clinical evidence of metastatic disease) has significantly increased during the past 5 to 10 years.

These patients present the physician with a dilemma. They have an incurable disease but no symptoms. Moreover, they are frequently well educated and motivated Internet users. Understandably, they are interested in attempting to alter the natural course of their disease, and they often come to us asking for various treatments that they have heard about. The dilemma is that there are no data to drive decisions.

Second-line hormonal therapies that have been used in this patient population include megesterol acetate, ketoconazole, aminoglutethimide, estrogens, and glucocorticoids.[8] Using PSA as an indicator of disease response in these patients may be problematic because in vitro data suggest that some agents (such as the growth factor inhibitor suramin) may affect cellular PSA production so that it is no longer concordant with tumor growth.

EXPERIMENTAL THERAPIES

Given the known adverse physical and psychological effects of castration and the adverse effects of LHRH analogs and combination therapy, various new approaches are being evaluated. These include antiandrogen monotherapy and intermittent therapy.

Antiandrogen monotherapy

When antiandrogens are used as single agents, testosterone levels typically remain at normal levels or increase slightly. Several small randomized trials suggested that some antiandrogens used in higher-than-standard doses may be equally as effective as castration. However, this issue remains controversial, and the use of antiandrogens as single agents cannot be considered the standard of care.[10]

Intermittent hormonal therapy

Several small clinical case series showed that intermittent hormone therapy (cyclical use and withdrawal of antiandrogens) may delay the time to androgen independence. Data from in vitro and animal models suggest that it also promotes cell death and tumor control.

Several large randomized clinical trials comparing standard hormone therapy to intermittent androgen deprivation are underway. However, even if this experimental approach is proven to be therapeutically equivalent to continuous hormonal therapy in terms of time to disease progression and survival, intermittent therapy may be better for patients. Quality of life may be significantly improved during the times when no hormone therapy is given, and it may decrease medication costs.

MANAGING HOT FLUSHES

No discussion of hormone therapy for prostate cancer would be complete without a brief review of the therapies used to control the main adverse effect—hot flushes—which can greatly affect a patient's quality of life. Although suppression of serum testosterone is a major factor in the development of hot flushes in men, the exact levels to which testosterone must be suppressed before hot flushes occur is unclear. What is known however, is that physiologic decreases in testosterone associated with aging rarely cause hot flushes.

In one study, megestrol acetate reduced hot flushes by 87%

In contemporary studies of patients undergoing androgen deprivation therapy for prostate cancer, almost three quarters of men reported distressing hot flushes that began 1 to 12 months following the start of therapy and continued for a mean of 30 months or until death.[11]

Historically, estrogens and estrogen-related drugs (eg, diethylstilbestrol [DES]) have been used to alleviate hot flushes. However, the propensity of estrogens to increase the risk of cardiovascular morbidity and current requirements for parenteral administration (oral DES is no longer commercially available) have limited the utility of these agents.

Today, the following treatment options are used to control hot flushes:

- Megestrol acetate (Megace) in low doses (40 mg/day); in a placebo-controlled, crossover clinical trial, it reduced hot flushes by 87%.[12]
- Venlafaxine (Effexor) is a novel antidepressant that inhibits neuronal serotonin and norepinephrine uptake. In a pilot trial that used a very low dose, 10 of 16 patients experienced a significant decrease in the frequency and severity of hot flushes. Therapy was relatively well tolerated.[13] A dose-finding, placebo-controlled trial is ongoing.
- Clonidine (Catapres) has been proposed, but several prospective trials have shown limited efficacy.[14]

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