

SECONDARY HORMONAL THERAPIES IN THE TREATMENT OF PROSTATE CANCER

WILLIAM K. OH

ABSTRACT

Patients with androgen-independent prostate cancer demonstrate progression of disease, despite chemical or surgical castration, and have a poor prognosis. Cancer progression may be manifest as an asymptomatic increase in serum prostate-specific antigen (PSA) or may be accompanied by symptomatic and/or radiographic evidence of tumor growth. Observation remains a reasonable choice for asymptomatic patients. However, many patients remain anxious about withholding further treatment and, although studies have not demonstrated a survival benefit with second-line hormonal therapy, it may be appropriate to consider these therapies. In patients who have radiographic and/or symptomatic progression, the use of second-line hormonal therapy is more easily justified. Treatment options include: (1) secondary use of antiandrogens (eg, high-dose bicalutamide), (2) therapies targeted against adrenal steroid synthesis (eg, ketoconazole, aminoglutethimide, and corticosteroids), and (3) estrogenic therapies (eg, diethylstilbestrol). Symptomatic improvement and PSA-level decreases of $\geq 50\%$ have been reported in approximately 20% to 80% of patients with androgen-independent prostate cancer who receive such second-line hormone therapies, with a typical response duration of 2 to 6 months. Toxicity is generally mild for these oral therapies, although serious side effects, including adrenal insufficiency, liver toxicity, and thrombosis, may occur. In conclusion, secondary hormonal therapies have a significant role in the treatment of patients with androgen-independent prostate cancer. Further research is needed to understand their optimal use. *UROLOGY* **60** (Suppl 3A): 87-93, 2002. © 2002, Elsevier Science Inc.

In 2001, >31,000 men are projected to die of prostate cancer, the second-leading cause of cancer death in men in the United States.¹ Although most of these men respond initially to androgen deprivation therapies (ADT), such as bilateral orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonists, patients eventually progress to an androgen-independent state in which the initial ADT regimen is no longer adequate to control disease.² The median duration of survival of patients with metastatic androgen-independent prostate cancer is approximately 1 year.³

Although most men with androgen-independent prostate cancer eventually develop symptoms related to metastases, often, the first indication of disease progression is an asymptomatic increase in serum prostate-specific antigen (PSA) levels noted during routine surveillance. Although there is no

evidence that secondary hormonal therapies or chemotherapy improve survival, patients and physicians often pursue treatment, despite a lack of symptoms. Physicians and their patients might initiate therapy because of concerns over impending symptoms, rapidity of increase of PSA levels, patient anxiety about observation alone, or the physician's belief that treatment may improve the patient's outcome. An important concern of this more aggressive approach is that the treatment may have a significant effect on quality of life, and therefore simpler treatments with less toxicity would be considered preferable in asymptomatic patients.⁴

In contrast, there is more evidence that treatment can palliate symptoms for patients with advanced disease. Despite this evidence, the lack of a documented survival benefit and concerns about toxicity leave many unanswered questions. Which therapies should be used and when? What is an acceptable level of toxicity? What is the psychological impact for patients of waiting without therapy? Is there an ability to predict response and to select appropriate patients for different approaches? In

From the Department of Adult Oncology, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA

Reprint requests: William K. Oh, MD, Dana-Farber Cancer Institute, 44 Binney Street, Boston, Massachusetts 02115. E-mail: william_oh@dfci.harvard.edu

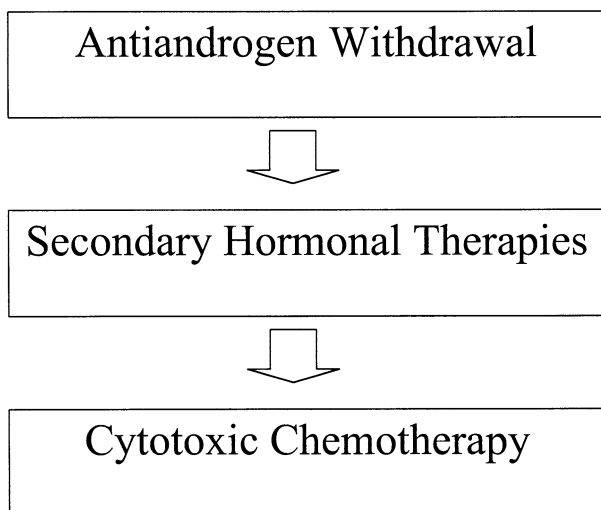


FIGURE 1. A typical treatment strategy for patients with androgen-independent prostate cancer.

particular, the timing of cytotoxic chemotherapy versus secondary hormonal therapies remains controversial and poorly studied.² In our institution, our practice is generally to start with secondary hormonal therapies in asymptomatic or minimally symptomatic patients and to proceed to chemotherapy as such treatments fail. However, there are some patients whose androgen-independent disease progresses rapidly enough that immediate institution of chemotherapy may be appropriate.

In general, a reasonable stepwise approach is to consider the easiest and least toxic interventions first, thus reserving chemotherapy for patients who have failed secondary hormonal therapies (Figure 1). Patients who are receiving antiandrogen therapy at the time of progression are monitored for signs of antiandrogen withdrawal syndrome. Subsequent treatment options may include (1) second-line antiandrogens, (2) adrenal androgen inhibitors, and (3) estrogenic therapies (Figure 2).

ANTIANDROGEN WITHDRAWAL SYNDROME

In 1993, clinical and PSA responses were reported in men who discontinued the antiandrogen flutamide upon developing progressive disease.⁵ This antiandrogen withdrawal syndrome was an important discovery in interpreting clinical trials and treating patients. In 3 separate studies of 138 patients, 29 (21%) had a PSA level decrease of $\geq 50\%$ after stopping flutamide.⁶ Generally, duration of response is 3 to 5 months, although responses > 2 years have been seen. Such withdrawal responses also have been reported after treatment with bicalutamide and megestrol acetate.^{7,8} A proposed mechanism to account for the antiandrogen withdrawal syndrome is the paradoxical activation

of mutant androgen receptors. Taplin *et al.*⁹ reported mutations in androgen receptors in 5 of 16 patients receiving combined androgen blockade versus only 1 of 17 receiving LHRH monotherapy, suggesting a selection for mutant receptors in patients exposed to antiandrogens. In addition, it has also been demonstrated that antiandrogens may activate prostate cancer cells harboring mutant androgen receptors.¹⁰

The Cancer and Leukemia Group B (CALGB) studied this phenomenon in a randomized, prospective trial (9583) of antiandrogen withdrawal alone compared with antiandrogen withdrawal plus high-dose ketoconazole.¹¹ In the antiandrogen withdrawal-alone arm, a $\geq 50\%$ PSA response was seen in only 13% of patients, with an objective response rate of 4% (Table I). In a correlative science companion study (CALGB 9663), 194 bone marrow biopsies were performed, 48 (25%) of which had evidence of cancer. In a preliminary abstract, of 27 patients for whom androgen receptor messenger RNA (mRNA) and PSA data were available, only 6 patients had detectable androgen receptor mutations. Of these, 1 (4%) had an antiandrogen withdrawal response and 5 (19%) had no antiandrogen withdrawal response. The conclusion of this correlative study was that androgen receptor mutations are not, in fact, responsible for the antiandrogen withdrawal response.¹²

SECOND-LINE ANTIANDROGENS

Bicalutamide is a nonsteroidal antiandrogen with dose-response effects in normalizing PSA levels in androgen-dependent prostate cancer. Patients with androgen-independent prostate cancer treated with high doses (150 to 200 mg) of bicalutamide have PSA decreases of $\geq 50\%$ in 20% to 24% of cases, with most responses seen in those who received prior flutamide therapy (Table II).¹³⁻¹⁵ It is not known why patients with prior flutamide treatment might have higher response rates to second-line bicalutamide, although it has been theorized that a mutant androgen receptor induced by prior flutamide therapy may mediate a higher response to salvage bicalutamide. The results of the study by Kucuk *et al.*¹⁴ suggest, however, that this is not the case. Treatment is oral and well tolerated, with the most common side effects being hot flashes (23%) and nausea (21%). However, treatment is expensive (approximately \$1000 per month) and is associated with a low response rate.

Megestrol acetate is a steroidal antiandrogen with progestational activity. Its antiandrogenic effects are not promising in treating androgen-independent patients, with objective response rates of 0% to 9%. A recent randomized study of 149 men randomized to low or high doses of megestrol ace-

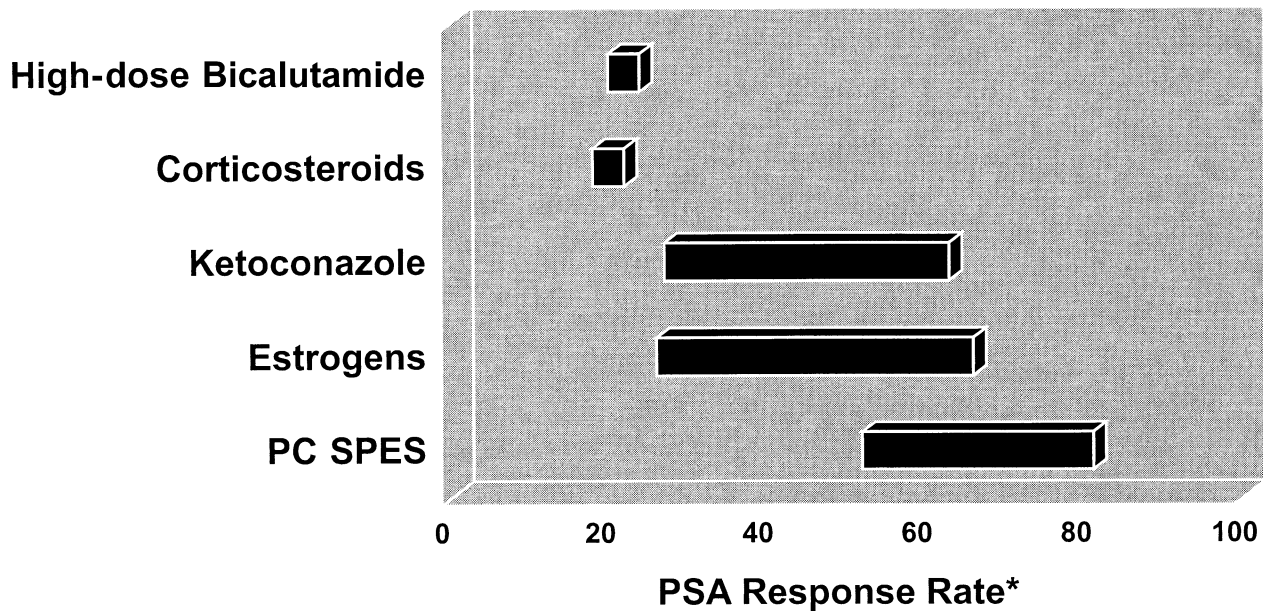


FIGURE 2. Secondary hormonal therapies for androgen-independent prostate cancer. *Prostate-specific antigen (PSA) response rate represents reported PSA decreases of $\geq 50\%$ in phase 2 clinical trials. Bars represent range of PSA decline rates in different clinical trials using bicalutamide (Casodex; AstraZeneca, Wilmington, DE), PC SPES (herbal compound; BotanicLab, Brea, CA), and other drugs.

TABLE I. CALGB 9583: randomized trial of antiandrogen withdrawal (AAW) versus antiandrogen withdrawal plus high-dose ketoconazole (HDK)¹¹

| | AAW Alone (n = 132) | AAW + HDK (n = 128) | P-Value |
|--------------------------|------------------------|---------------------------|---------|
| $\geq 50\%$ PSA response | 13% | 27% | 0.012 |
| Objective response | 4% | 13% | 0.016 |
| Survival | 16 mo | 15 mo | 0.795 |
| Grade 3,4 toxicity | 4% | 22% | 0.001 |

PSA = prostate-specific antigen.

tate reported PSA decreases only 8% to 13% of the time and rare objective responses.¹⁶ Side effects included thrombophlebitis and fluid retention. Based on these results, megestrol acetate has limited anti-tumor activity in androgen-independent prostate cancer and should not be used for this indication.

LOW-DOSE CORTICOSTEROIDS FOR PROSTATE CANCER

Low-dose corticosteroids inhibit adrenocorticotropic hormone secretion through a negative feedback loop, which thereby decreases adrenal androgen production. Tannock *et al.*⁴ reported a significant palliative response with 10 mg of prednisone in a phase 2 trial of 37 patients. In 2 subsequent, large, randomized studies of mitoxantrone plus steroids versus steroids alone, the steroid arm was associated with more modest palliative bene-

fits. In a Canadian randomized trial of prednisone 10 mg daily versus prednisone plus mitoxantrone, a significant pain response was seen in 12% of patients, lasting only 18 weeks, in the prednisone arm.¹⁷ Furthermore, PSA level decreases of $\geq 50\%$ were seen in only 18% of these patients. CALGB found similar results in 123 patients randomized to an arm of daily hydrocortisone 40 mg alone, with a significant reduction of pain in only 8% and a PSA response rate of 22%.³ Low doses of dexamethasone have also been reported to have significant palliative and objective benefit. In a recent study of 37 men with hormone-refractory disease, 62% had a PSA level decrease of $\geq 50\%$. In addition, improvements in bone scans and symptoms were noted.¹⁸ In summary, low-dose corticosteroids have a modest role in the management of androgen-independent prostate cancer. Although orally adminis-

TABLE II. High-dose bicalutamide for androgen-independent prostate cancer

| Study | N | Dose (mg) | ≥50% PSA Response | ≥50% PSA Response in Patients with No Prior Flutamide |
|--|----|-----------|-------------------|---|
| Scher <i>et al.</i> (1997) ¹⁵ | 51 | 200 | 24% | 15% |
| Joyce <i>et al.</i> (1998) ¹³ | 31 | 150 | 23% | 6% |
| Kucuk <i>et al.</i> (2001) ¹⁴ | 52 | 150 | 20% | 20% |

PSA = prostate-specific antigen.

TABLE III. High-dose ketoconazole plus hydrocortisone for androgen-independent prostate cancer

| Study | N | Dose (mg tid) | ≥50% PSA Response |
|---|-----|---------------|-------------------|
| Small <i>et al.</i> (1997) ²¹ | 48 | 400 | 63% |
| Millikan <i>et al.</i> (2001) ²² | 45 | 400 | 40% |
| Small <i>et al.</i> (2001) ¹¹ | 128 | 400 | 27% |
| Harris <i>et al.</i> (2001) ²³ | 22 | 200 | 55% |

PSA = prostate-specific antigen.

tered, inexpensive, well-tolerated, and associated with objective benefit, the overall response rate is low enough and duration of response short enough that this therapy might be considered only after more effective secondary hormonal therapies have been tried.

INHIBITORS OF ADRENAL ANDROGEN PRODUCTION

Approximately 10% of circulating androgen in humans is secreted by the adrenal glands. In androgen-independent states, some tumor cells must retain sensitivity to androgens, because a further decrease in circulating androgen levels by bilateral adrenalectomy or by drugs that inhibit adrenal steroidogenesis can induce a clinical response.¹⁹ Aminoglutethimide, ketoconazole, and corticosteroids act primarily via this mechanism. In a review of 13 clinical trials of aminoglutethimide plus hydrocortisone, there was an overall partial response rate of 9%.²⁰ Aminoglutethimide toxicity includes fatigue, nausea, skin rash, orthostatic hypotension, and ataxia.

Ketoconazole is similarly effective in suppressing testicular and adrenal androgen production. In vitro experiments also suggest a possible direct cytotoxic effect of ketoconazole on prostate cancer cells.²¹ A review of 10 older studies in androgen-independent prostate cancer using high-dose ketoconazole plus replacement hydrocortisone showed measurable responses in approximately 15%.²⁰ There are 3 more recent trials of high-dose ketoconazole that demonstrate much higher response rates when using PSA endpoints (Table III).^{11,22,23}

Small *et al.*²² treated 48 patients with 400 mg 3 times daily in a phase 2 trial and found PSA decreases of ≥50% in 63%. In another trial of 45 patients treated with high-dose ketoconazole, Millikan *et al.*²³ showed a 40% PSA response rate using a similar dose. In the previously mentioned CALGB trial (9583), the arm that received concurrent antiandrogen withdrawal and high-dose ketoconazole demonstrated a 27% PSA response rate and a 13% measurable response rate, both significantly greater than the antiandrogen withdrawal-alone arm (Table I).¹¹

Increased gastric pH decreases drug absorption, so ketoconazole should be taken on an empty stomach and, if possible, in the absence of histamine-2 blockers or antacids. Although toxicity is generally mild or moderate, including nausea, diarrhea, fatigue, and skin changes, some patients require discontinuation of the drug because of toxicity. A recent phase 2 study suggests that similar response rates may be obtained with half the traditional dose (ie, 200 mg 3 times daily), with fewer apparent side effects (Table III).²⁴

ESTROGENIC THERAPIES

Estrogenic therapies can induce secondary responses in patients with apparent androgen-independent prostate cancer, suggesting an additional mechanism of action beyond suppression of the pituitary–gonadal axis. Several modern series suggest that diethylstilbestrol (DES) and other estrogens can produce PSA responses in a significant proportion of patients with androgen-independent prostate cancer (Table IV).^{25–28} The mechanism for

TABLE IV. Estrogenic therapies in androgen-independent prostate cancer

| Study | N | Type (Daily Dose) | >50% PSA Response |
|---|-----|-------------------|-------------------|
| Smith <i>et al.</i> (1998) ²⁵ | 21 | DES (1 mg) | 43% |
| Rosenbaum <i>et al.</i> (2000) ²⁴ | 18 | DES (3 mg) | 66% |
| Shahidi <i>et al.</i> (2001) ²⁷ | 127 | DES (1 mg) | 26% |
| | 115 | DES (3 mg) | 32% |
| Pfeiffer <i>et al.</i> (1999) ³⁴ | 16 | PC SPES (9 caps) | 81% |
| de la Taille <i>et al.</i> (2000) ³¹ | 22 | PC SPES (3 caps) | 66% |
| Small <i>et al.</i> (2000) ³⁵ | 37 | PC SPES (9 caps) | 54% |
| Oh <i>et al.</i> (2001) ³³ | 23 | PC SPES (6 caps) | 52% |

Caps = capsules; PSA = prostate-specific antigen.

the effect is unclear, but may represent a direct cytotoxic effect on the cells, perhaps through an apoptotic mechanism.²⁹ In 3 recent reports, it is suggested that doses of DES from 1 to 3 mg may cause PSA responses in androgen-independent prostate cancer in 26% to 66% of those treated.^{25,26,28} In the first study outlining this effect, Smith *et al.*²⁶ demonstrated a 43% PSA response rate. This group noted that responses were unlikely after prior treatment with ketoconazole, although subsequent reports have not confirmed this finding.

PC SPES (BotanicLab, Brea, CA)* is an herbal combination with 8 different components, including saw palmetto, licorice, pseudoginseng, and skullcap.³⁰ Preclinical and clinical studies of PC SPES have demonstrated significant antitumor activity and strong estrogenic effects.^{31–33} Using high-performance liquid chromatography and mass spectroscopy/gas chromatography in an attempt to identify known estrogens, DiPaola *et al.*³³ did not identify DES, estradiol, or estrone in an extract of PC SPES. There have been 4 clinical studies of PC SPES in androgen-independent prostate cancer, all demonstrating high PSA response rates (ranging from 52% to 81%) and toxicities similar to estrogen therapy, including thrombotic complications in 4% to 6% and breast swelling or tenderness in most patients.^{32,34–36} Important

* After the time of this writing, in February 2002, the California Department of Health and the US Food and Drug Administration reported the detection of warfarin in PC SPES and the product was voluntarily recalled. As of June 2002 BotanicLab ceased producing PC SPES, and it is no longer available in the United States.

questions remain about the role of PC SPES in the management of androgen-independent prostate cancer and, perhaps most significantly, the identification of the active ingredient(s) of PC SPES.

CONCLUSION

Secondary hormonal therapy for prostate cancer represents an important group of therapies for a group of patients with a limited prognosis. Although many important issues remain unanswered about the optimal use of these treatments, multiple phase 2 trials have demonstrated that PSA and clinical responses can be seen with these treatments in significant proportions of androgen-independent prostate cancer patients. Interpretation of phase 2 trials must be done carefully in this setting, because comparisons between trials may be invalid and because objective and PSA responses must be kept distinct. Nonetheless, no study has yet demonstrated a survival benefit with the use of these treatments, which can be expensive as well as toxic, with a potential negative effect on quality of life, particularly in patients who have minimal or no symptoms. Cost is especially critical to consider when prescribing these oral medications, as many elderly patients have inadequate or no prescription drug coverage.

Despite this, patients appear to benefit from therapy in several ways. Clearly, symptomatic patients have had palliative responses to treatment. Other patients may have a delay in progression of their disease. Patients are also relieved if their increasing PSA level is effectively reversed; this important psychological effect deserves further study. Finally, patients have few good treatment alternatives to secondary hormonal therapies. Chemotherapy, although active and generally well tolerated, has a less favorable side-effect profile in general.² Radiopharmaceuticals or external-beam radiotherapy may benefit patients with symptomatic disease, but may have limited efficacy and potentially serious toxicity.

Further research needs to continue in defining the optimal use of secondary hormonal therapies, including the appropriate timing and sequencing of treatments. Furthermore, more randomized trials are needed to compare treatments and to evaluate survival benefits, if any, to these treatments.

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