Original Article

The Selection of Hormonal Therapy in Prostate Cancer: Who, When, and for How Long?

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Key Words

Prostate cancer, combined androgen blockade, hormone therapy, androgen deprivation, secondary hormonal therapy, ketoconazole

Abstract

Androgen deprivation is the foundation for the systemic therapy of advanced prostate cancer. Multiple trials have tested combined androgen blockade versus androgen deprivation alone in patients with advanced disease. These studies suggest a slight advantage to the combined approaches that contain flutamide and bicalutamide, but the lack of dramatic differences in outcome makes monotherapy reasonable, especially in patients with more indolent disease. Intermittent androgen deprivation is an alternative that may allow patients to reduce the total time on androgen suppression as well as possibly delay the onset of androgen independence. A number of secondary hormonal therapies, including deferred and secondary antiandrogens, ketoconazole, and estrogens have shown modest response proportions. Patients with less advanced disease such as a rising prostate-specific antigen have varied outcomes, and no standard approach exists. In this group, noncastrating forms of hormonal therapy are being evaluated. Patients undergoing definitive local therapy who have high-risk features may benefit from early, as opposed to deferred, androgen deprivation. This review examines the evidence for the current state of the art in hormonal therapy in patients with prostate cancer and focuses, in particular, on treatment composition and timing as well as the rationale for the use of hormonal therapy in early stage disease. (*JNCCN* 2004;2:261–268).

Sixty years after the first description by Huggins and Hodges that castration resulted in significant clinical responses in men with metastatic prostate cancer,[1] androgen deprivation (AD) remains the cornerstone of therapy for advanced prostate cancer and one of the most effective therapies in solid tumor oncology (Table 1). Despite this, AD is not curative for patients with advanced disease, because prostate cancer adapts to the androgen-deprived milieu. Consequently, current research seeks to define the optimal timing of therapy, its use in patients with nonmetastatic disease, and the most appropriate components of an effective hormonal regimen (Table 2). A number of developments in the past decade have resulted in increased use of intermittent AD, as well as "potency preserving" therapy. A critical review of issues regarding patient selection and the duration and timing of hormone therapy is required to optimize clinical outcomes.

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Hormonal Therapy in Advanced Prostate Cancer

Patients who require AD most immediately are those with metastatic disease resulting in bone pain or organ dysfunction. The best composition of initial hormonal therapy is controversial, however. In the United States, the principal form of AD is undertaken with a leuteinizing hormone-releasing hormone (LHRH) agonist such as leuprolide, goserelin, or triptorelin. Recently, the Food and Drug Administration approved an LHRH antagonist, abarelix (Plenaxis, Praecis Pharmaceuticals, Waltham, MA), with an indication for inducing castration in men with advanced prostate cancer with compressive neurologic symptoms, bladder outlet obstruction, or pain from metastatic disease requiring opioid analgesics. The putative advantage of this approach is that, with a direct LHRH antagonist, castrate levels of testosterone are

Table 1 Terminology of Hormonal Therapy in Prostate Cancer	
Androgen deprivation (AD):	Therapy that reduces levels of circulating testosterone to castrating levels (typically < 50 ng/mL)
Combined androgen blockade (CAB):	Therapy that uses AD simultaneously with an antiandrogen. This approach reduces circulating testosterone and blocks the effects of testosterone at the level of the androgen receptor within the cancer cell itself.
Intermittent androgen deprivation (IAD):	Use of AD or CAB for a proscribed period of time (typically 6-12 months) then discontinuing. Typically, hormonal therapy is restarted when PSA levels have reached a certain point.
Antiandrogen monotherapy:	This refers to the use of an antiandrogen without AD. This has been proposed as a means of delivering hormonal therapy without the side effects of AD.
Androgen-independent prostate cancer	Prostate cancer that has progressed despite AD but still may be sensitive to other hormonal manipulations (eg, a second antiandrogen or ketoconazole)
Hormone refractory prostate cancer	Prostate cancer that no longer responds to any hormonal therapies.

achieved without the risk of a potentially dangerous tumor "flare" seen with the surge in testosterone seen with LHRH agonists. However, such flare phenomena are also well controlled with the short-term use of an oral antiandrogen such as flutamide, bicalutamide, or nilutamide.

Initial Therapy in Advanced Disease: Monotherapy or Combined Blockade?

The question of combined androgen blockade (CAB) versus LHRH monotherapy in metastatic disease has been addressed in a number of studies. In a multicenter randomized clinical trial in the United States, 300 patients with previously untreated metastatic disease received leuprolide plus placebo and 303 received leuprolide plus flutamide. An advantage in progression-free survival (16.5 vs. 13.9 months; $P = .039$) as well as median survival (35.6 vs. 28.3 months; $P = .035$) was seen in favor of combined treatment.[2] A subsequent study randomized 1,387 patients to bilateral orchiectomy plus either placebo or flutamide. In this study, no difference was seen with respect to overall survival ($P = .14$). Furthermore, flutamide resulted in increased anemia and diarrhea as well as a decreased overall quality of life.

Although these two large placebo-controlled studies reached divergent conclusions, a total of 27 randomized trials using combinations of orchiectomy, goserelin, leuprolide combined with flutamide, cyproterone acetate, nilutamide, or placebo have been conducted. In 1995, the Prostate Cancer Clinical Trialists' Collaborative Group published a meta-analysis of 22 such trials. In this analysis, 5-year survival for patients receiving an antiandrogen was 25.4%. That number was not significantly better than the 23.6% found for patients receiving gonadal androgen suppression alone.[3]

A second report from this group was published in 2000.[4] In this report, 27 trials involving 8,275 men and 5,932 deaths (80% from prostate cancer) were included. In the analysis comparing CAB with gonadal AD alone, CAB improved 5-year survival by 1.8%, with a confidence interval (CI) of 0% to 5% ($P = .11$). The differences were significant, however, for regimens that included flutamide and nilutamide compared with those with cyproterone acetate (5-year survival, 27.6% vs. 24.7%; logrank $P = .005$).

Data from 20 trials reported in a third meta-analysis published in 2002 indicated no advantage to CAB when measured at 2 years (hazard ratio [HR], 0.97; 95% CI, 0.866–1.087), but did show an advantage in

Table 2 Hormonal Therapies Used in Prostate Cancer

Gonadal Androgen Deprivation	Antiandrogens
• LHRH Agonists	• Bicalutamide
Leuprolide	• Flutamide
Goserelin	• Nilutamide
Triptorelin	• Cyproterone
• LHRH Antagonists	
Abarelix	
• Orchiectomy	
Adrenolytics	Estrogens
• Ketoconazole	• Diethylstilbestrol
• Aminoglutethimide	
Corticosteroids	Progestins
• Prednisone	• Megestrol
• Hydrocortisone	
• Dexamethasone	

favor of combined blockade at the 5-year time point (HR, 0.871; 95% CI, 0.805–0.942) in the 10 studies analyzed. Taken together, these analyses of several thousand patients suggest that outcomes with CAB are slightly better than those with monotherapy and that CAB appears to be associated with slightly more toxicity. Furthermore, the steroidal antiandrogen cyproterone acetate appears to be inferior to the nonsteroidal antiandrogens flutamide, bicalutamide, and nilutamide, based on these results.

Intermittent Versus Continuous Hormonal Therapy

Although few argue the need for AD in patients with advanced disease, the optimal duration of therapy is not clearly defined. The concept of intermittent androgen blockade (IAB) evolved from laboratory studies with the Shinogi mouse model showing that prostate stem cells can survive initial castration and that continued exposure to androgen delayed the development of androgen independence. Therefore, in addition to potentially improving quality of life and reducing cost, investigators hypothesize that IAB may delay progression to androgen independence.

In 1995, Goldenberg et al.[5] reported an initial experience with 47 patients using this approach. After 6 months of AD, patients were seen until the prostate-specific antigen (PSA) levels increased to between 10 and 20 ng/mL. The first two treatment cycles (time from start of therapy until restarting androgen deprivation) lasted 73 and 75 weeks, respectively, and 41% and 45% of the cycle was spent off therapy, respectively. Testosterone returned to normal by 8 weeks, and sexual function returned in 90% of patients during the periods off therapy.[5]

An update of this experience with 102 patients was reported in 2003. The average time off therapy after cycle 1, 2, and 3 was 13, 11, 10, and 8 months, respectively. A trend toward prolongation of time to progression and time to death when compared with contemporary studies of continuous AD was seen.[6] Grossfeld et al.[7] at the University of California San Francisco reported a similar experience with 61 patients on intermittent therapy. In that study, patients spent an average time of 45% off hormone therapy. Similar to prior studies, time off therapy decreased with each successive cycle of hormonal ablation.[7]

Assessing whether these data support the biologic hypothesis on which they are based is difficult, and randomized comparative data will be required. Two phase III trials are underway, one in nonmetastatic prostate cancer, led by the National Cancer Institute of Canada, and the other in patients with metastatic disease, led by the Southwest Oncology Group (SWOG).

Secondary Approaches after Initial Hormone Failure

The assessment of response and progression after initial AD is complicated by tumor heterogeneity and the observation that changes in PSA frequently predate changes in imaging studies. Many investigators have shown that a decline by 50% or greater in PSA after starting therapy is associated with improvement in outcome,[8–11] raising the possibility that PSA declines can be used as a surrogate marker of response. As a result, consensus criteria for the use of PSA as a measurement of response have been developed.[12] These suggest that a decline in PSA by 50% confirmed by a second PSA value 4 or more weeks later may be considered a "response." These criteria eliminate the requirement for measurable disease, which is often absent in androgen-independent prostate cancer.

Antiandrogen Withdrawal Phenomenon

Clinical responses after antiandrogen withdrawal (AAWD) were first reported with flutamide in 1993[13] and have subsequently been described after other agents, including bicalutamide, nilutamide, megestrol acetate, and diethylstilbesterol.[14–17] Although initial studies indicated that this phenomenon may occur in as many as 25% of patients,[13] a recent large prospective study reported a PSA decline of 50% or more in only 13% of patients. Objective tumor responses occurred in only 2%.[18] Despite this low overall response proportion, AAWD is mandated after progression on an antiandrogen before starting further therapy.

Secondary Hormonal Agents

The use of antiandrogens as second- and third-line therapy produces responses in approximately 20% to 50% of patients. This approach is supported by in vitro experimentation in which growth of the LNCaP prostate cancer cell line was inhibited by bicalutamide despite the fact that flutamide acted as a partial agonist.[19] The use of high-dose bicalutamide (200 mg/d) has been shown to produce responses in 14% of patients with disease progression on flutamide and to occur irrespective of whether patients had previously experienced an AAWD response.[20]

One study of 150 mg of daily bicalutamide, however, showed PSA declines of 50% or greater in 23% of patients,[21] and a prior AAWD response was predictive of a response to the second antiandrogen. One retrospective analysis of 14 patients treated with nilutamide revealed that 50% of patients treated with this drug after progression on another antiandrogen experienced a 50% or greater decline in PSA for a median duration of 11 months.

Kassouf et al.[22] reported sustained PSA declines of 50% or more in 29% of patients taking nilutamide after progression on an antiandrogen. Furthermore, all five (100%) of the patients who had experienced previous AAWD responses also responded to nilutamide, in contrast to only 18% (3 of 17) of patients who did not have an AAWD response. Taken together, these data suggest that patients who respond to one antiandrogen are more likely to respond to secondary and tertiary drugs of this class. Furthermore, a prior response to AAWD appears to identify a group of patients who are more likely to respond to a second antiandrogen.

Adrenal Suppression

After gonadal androgen suppression, alternative androgens may continue to activate the androgen receptor (AR). The adrenal cortex is the primary source of the androgens dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione, all of which are capable of activating both wildtype and mutated androgen receptors. Clinical strategies targeting production of adrenal androgens have been explored using aminoglutethimide and ketoconazole.

Early studies of aminoglutethimide reported a PSA decline of over 80% in 48% of patients.[23] In a pilot study with ketoconazole, 20 consecutive patients with progressive disease despite CAB were treated with ketoconazole and hydrocortisone (given as corticosteroid replacement) simultaneous with AAWD.[24] Eleven (55%) patients experienced a 50% or greater decline in PSA, and the median duration of response was 8.5 months. When ketoconazole was used after progression despite AAWD, a response proportion of 62.5% was seen.[25]

These findings led to a randomized trial of AAWD alone or in combination with high-dose ketoconazole/hydrocortisone conducted by the CALGB. The PSA response proportion to those undergoing AAWD alone was 13%, compared with 30% in those receiving ketoconazole/AAWD ($P \leq .001$).[18] Fourteen percent of patients treated with ketoconazole/AAWD experienced objective responses. The percentage of patients who experienced a 50% or greater decline in PSA was substantially smaller than in previous studies. This may reflect the propensity for selection bias seen in single institutional studies, but may also reflect a decreased bioavailability of ketoconazole that occurs when the drug is taken with food or in the presence of a less than optimally acidic environment, such as in combination with antacids. This is in contrast to prior studies that mandated that ketoconazole be taken on an empty stomach and forbade the use of antacids, proton pump inhibitors, or H2 blockers. Nevertheless, these data suggest that ketoconazole is a modestly active drug in patients with progressive disease on CAB.

Estrogens

Estrogens have modest efficacy in hormone refractory prostate cancer. In one study, nine of 21 (43%) patients treated with 1 mg/d of diethylstilbestrol (DES) developed a significant PSA response, and a higher rate of response was seen in those who had received only one prior hormonal therapy (62%) versus 13% of those who had received more than one prior hormone theropy.[26] In a study in which DES at an oral dose of 3 mg daily was used as the control arm, a 21% rate of PSA response by consensus criteria was reported.[27] Taken in aggregate, these data suggest that estrogens have some activity in patients with progressive disease despite antiandrogens and should be considered a therapeutic option.

The androgen-deprived milieu after AD creates an estrogen-predominant microenvironment. This raises the question of whether estrogen inhibitors might have antitumor effects. Tamoxifen was studied in the early 1980s and found to be associated with a 23% overall response rate. However, this trial included both hormone-refractory and hormone-naïve patients, and it was performed before the era of PSA endpoints.[28] The combination of vinblastine and tamoxifen was studied in patients with hormone-refractory disease, and no partial or complete responses were seen.[29] High-dose tamoxifen (160 mg/m^2/d) has been evaluated and showed a combined partial response/stable disease rate of 23%.[30]

The selective estrogen receptor modulator raloxifene has shown preclinical activity in prostate carcinoma models and is currently being evaluated in clinical trials. Aromatase inhibitors have not shown any activity.[31,32] Abrogation of the effects of estrogen, therefore, continues to be an area of investigation, with mixed results seen to date in small clinical trials.

Corticosteroids

Numerous studies have described the antitumor effects of corticosteroids. Tannock et al.[33] treated 37 patients with hormone-refractory prostate cancer (HRPC) with daily oral prednisone in doses ranging from 7.5 to 10 mg/d. After one month of therapy, improvements in quality of life were noted in 38% of the patients, and this effect was maintained for a median of 4 months in 19% of the patients. Kelly et al.[34] reported a 50% decline in PSA lasting a median duration of 4 months in 20% of patients treated with hydrocortisone at a dose of 40 mg daily.

In a randomized study of suramin versus placebo, 38 of 230 (16%) patients with hormone-refractory prostate cancer who received 30 mg/d of hydrocortisone and no other treatment had a greater than 50% reduction in PSA. A similar outcome was seen in 22% of patients in the hydrocortisone control arm of a randomized trial comparing this drug alone or in combination with mitoxantrone.[35]

Hence, most trials have shown modest (10%–20%) PSA response proportions. One outlying trial was reported by Storlie et al.,[36] in which PSA reductions were seen in 61% of 38 patients treated with 0.75 mg of dexamethasone three times daily. Among responders, 35% had objective responses on radiographic studies. Confirmatory studies are required. Taken together, these data suggest modest antitumor effects from corticosteroids.

The role of progesterone in the treatment of HRPC is modest. Megestrol acetate, a progestin agonist, has been associated with a PSA response proportion of approximately 10% to 15%. These effects may occur through suppression of LHRH, blockade of the AR, and possibly through inhibition of 5-alpha reductase.[16,37] A randomized trial of low-dose (160 mg/d) versus high-dose (640 mg/d) megestrol acetate was conducted by the CALGB.[38] In this study, no significant difference was seen in survival (11.2 vs. 12.1 months, respectively), and the PSA response proportion was 13.8% for the low-dose arm and 8.8% for the high dose-arm. Serologic responses have also been reported to occur on withdrawal of megestrol.[16]

Use of Hormonal Therapy in Nonmetastatic Prostate Cancer

Given the significant benefits of AD in advanced disease, many have questioned whether its benefits may extend to patients with a lower burden of disease, such as those with localized disease or serologic (PSA) relapse after local therapy.

Localized Disease

A significant body of evidence suggests that those who are diagnosed with localized prostate cancer with unfavorable risk factors (high PSA, Gleason grade, or T stage) attain a disease-free and overall survival benefit from adjuvant AD. In such settings, the rationale for AD is twofold. First, AD may be an effective means of eliminating any occult micrometastatic disease. Second, for patients treated with radiation therapy, a synergy between the radiation and AD may lead to an improved cell kill.

Adjuvant Therapy

A randomized study from the Eastern Cooperative Oncology Group started in the 1980s randomized patients with pathologically proven pelvic lymph node metastases to receive immediate and lifelong AD versus AD started at development of radiographically-defined metastatic disease.[39] This study was designed and begun before widespread PSA testing, so a rising PSA after surgery was not used as a marker of progression. However, after 98 men were randomized, accrual slowed because of changes in practice occurring due to the onset of PSA testing. The accrual goal of the study was not met. Nevertheless, with a median duration of follow-up of 7.1 years, 7 of 47 (15%) men in the immediate therapy compared with 18 of 51 (35%) men in the deferred therapy group had died ($P = .02$) This study shows that earlier hormonal therapy is superior in terms of overall survival. However, in the current era, in which many treatment decisions are directed by rising PSA levels, the question is *how* early hormonal therapy should be started.

Noncastrating approaches after surgery have also been studied. In a series of trials reported recently, men who underwent RP were randomized to receive adjuvant high-dose bicalutamide (150 mg) or placebo for two years. With a median follow-up time of 3 years, a benefit in terms of time to objective disease progression has been reported for patients receiving bicalutamide.[40]

Similar results are available for patients who underwent definitive local radiotherapy. Individuals who received high-dose bicalutamide as part of a watchful waiting program, however, were found to have a higher death rate that those treated with placebo. These data

resulted in the withdrawal of approval for this indication in the United Kingdom and Canada.[41,42] The reason for this dichotomy is not clear, and further outcome data from this large trial are anticipated.

The combination of finasteride (5 mg twice daily) plus low-dose flutamide (125 mg twice daily) has also been studied in patients with PSA-only disease. The outcomes of 54 patients treated for a median of 44 months was recently reported. Of this group, 38% had sustained PSA levels below 0.4 ng/mL, 29% developed PSA progression and continued on therapy, and fewer than 10% had experienced and maintained a PSA reduction of 50% or greater (but did not reach levels below 0.4 ng/mL). As with high-dose bicalutamide, the main toxicities were gynecomastia and breast tenderness, occurring in a majority of patients, and gastrointestinal toxicity, occurring in 22%.[43] In summary, these results show modest activity to this approach, but further study is required to more clearly define it as an alternative to AD.

For patients treated with radiation therapy, much more definitive data indicate that adjuvant AD benefits those in the highest risk categories. Two major studies, EORTC 22863 (the "Bolla" study),[44] which compared 3 years of concurrent and adjuvant AD with deferred AD therapy, and RTOG 8531, which tested lifelong AD versus AD begun at clinical progression, support the use of adjuvant AD. In both studies, patient eligibility required large bulky primary tumors (T3 and T4) or high Gleason grade OR node positivity. The recent report of the 10-year outcomes of RTOG 8531 indicates a disease-specific (83% vs. 78%; $P = .0053$) and overall (47% vs. 38%; $P = .0043$) survival benefit in favor of immediate AD.[45] These data are of particular note because in RTOG 8531, the hormone therapy was strictly adjuvant, thereby eliminating the potential confounding variable of an interaction between radiation and androgen ablation.

Taken together, the results of the ECOG surgical adjuvant study authored by Messing and the radiation trials authored by Bolla and Pilepich[46] confirm the benefits of early AD in patients with high-risk localized and locally advanced prostate cancer who receive definitive local therapy.

Serologic Progression

The initiation of hormonal therapy for patients with a rising PSA as their only manifestation of disease recurrence is controversial. The natural history of these patients is heterogeneous, and no adequately powered, randomized clinical trial has been reported that definitively argues either for or against the use of hormonal therapy in patients with a rising PSA. The factors that are most likely to be associated with the development of metastatic disease, based on retrospective data, are a short time to PSA recurrence after definitive local therapy, a short PSA doubling time, and a high Gleason grade of the primary tumor.[47] A short PSA doubling time after definitive local therapy has recently been suggested as a surrogate for a prostate cancer-mediated death.[48]

With these considerations in mind, it may be appropriate to offer AD to patients with PSA-only disease who have a high likelihood of relapse based on the factors mentioned previously. Alternatives to full AD are desirable for many because they offer the potential for clinical benefit and avoid many of the side effects associated with full AD.

Conclusions

After 60 plus years, AD continues to be the basis for the systemic therapy of advanced prostate cancer. For patients with advanced disease, a slight advantage can be seen with the combined approach, but the lack of dramatic differences in outcome makes monotherapy reasonable in patients with more indolent disease. A number of secondary hormonal therapies such as second- and third-line antiandrogens, ketoconazole, and estrogens have shown modest activity. Patients undergoing definitive local therapy who have high-risk features may benefit from early, as opposed to deferred, AD. No standard approach exists for patients with serologic relapse, but retrospective data suggest that patients who relapse with a rapidly rising PSA are at high risk for death from prostate cancer.

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