# Secondary Hormonal Therapy for Advanced Prostate Cancer

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**Purpose:** Androgen ablation remains the cornerstone of management for advanced prostate cancer. Therapeutic options in patients with progressive disease following androgen deprivation include antiandrogen withdrawal, secondary hormonal agents and chemotherapy. Multiple secondary hormonal agents have clinical activity and the sequential use of these agents may lead to prolonged periods of clinical response. We provide a state-of-the-art review of the various agents currently used for secondary hormonal manipulation and discusses their role in the systemic treatment of patients with prostate cancer.
**Materials and Methods:** A comprehensive review of the peer reviewed literature was performed on the topic of secondary hormonal therapies, including oral antiandrogens, adrenal androgen inhibitors, corticosteroids, estrogenic compounds, gonadotropin-releasing hormone antagonists and alternative hormonal therapies for advanced prostate cancer.
**Results:** Secondary hormonal therapies can provide a safe and effective treatment option in patients with AIPC. The use of steroids and adrenolytics, such as ketoconazole and aminoglutethimide, has resulted in symptomatic improvement and a greater than 50% prostate specific antigen decrease in a substantial percent of patients with AIPC. A similar clinical benefit has been demonstrated with estrogen based therapies. Furthermore, these therapies have demonstrated a decrease in metastatic disease burden. Other novel hormonal therapies are currently under investigation and they may also show promise as secondary hormonal therapies. Finally, guidelines from the United States Food and Drug Administration Prostate Cancer Endpoints Workshop were reviewed in the context of developing new agents.
**Conclusions:** Secondary hormonal therapy serves as an excellent therapeutic option in patients with AIPC in whom primary hormonal therapy has failed. Practicing urologists should familiarize themselves with these oral medications, their indications and their potential side effects.

*Key Words: prostate, prostatic neoplasms, hormones, therapy, carcinoma*

In the United States an estimated 232,090 new cases were diagnosed and approximately 30,350 deaths were attributable to this disease in 2005.[1] Up to a third of patients treated for localized prostate cancer eventually experience biochemical recurrence. Most of these patients are placed on hormonal therapy with an LHRH agonist. Historically almost all patients with metastatic disease on primary hormonal therapy demonstrate evidence of hormonal resistance after an average of 18 to 24 months.[2] Unfortunately after hormone resistance occurs the prognosis in patients with metastatic, hormone refractory disease is dismal with a median survival of 12 to 18 months.[2] Due to a large subset of patients receiving hormonal therapy for biochemical failure a significant number of individuals now have AIPC without clinical evidence of metastatic disease. These patients are often anxious about their disease status and are typically highly motivated to receive additional therapy.

Most urologists are comfortable providing early treatment in patients with progressive disease through strategies such as the addition of a nonsteroidal antiandrogen or AAWD. However, after these basic hormonal manipulations have been exhausted almost all urologists defer to chemotherapy. While chemotherapy prolongs survival and improves quality of life, this strategy is more toxic and ignores the potential usefulness of secondary hormonal therapy (see Appendix). Secondary hormonal therapies have been shown to result in a greater than 50% decrease in PSA in a substantial percent of patients with AIPC and a prolonged clinical benefit in some (table 1). Despite these benefits urologists have been wary of implementing these therapies due to fear of toxicities, which have been demonstrated to be mild in numerous studies (table 2). Through this review we hope to demonstrate that secondary hormonal therapies can provide a safe and effective treatment option in patients with AIPC.

## PROGNOSTIC FACTORS

In most patients with progressive disease in the face of castrate levels of testosterone there are 3 potential courses of action, namely observation, secondary hormonal therapy and chemotherapy.[3] Observation while maintaining testosterone suppression is acceptable in patients with low PSA, prolonged PSA doubling time and no measurable metastatic disease. Some patients with metastases who have a low disease burden and slowly progressive disease may also be candidates for this approach. Prognostic models have been developed to assess patients who have progressive castrate metastatic disease despite initial hormonal therapy and they may be useful for determining whether to advance a

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TABLE 1. *Select trials of second line antiandrogens, adrenal androgen inhibitors, alternative steroid hormones and estrogenic compounds in AIPC*

| References | Treatment (dose) | No. Pts | % Greater Than 50% PSA Response | Median Response Duration (mos) |
|---|---|---|---|---|
| Second line antiandrogens: | | | | |
| Kucuk et al[18] | High dose bicalutamide (150 mg/day) | 52 | 20 | Not available |
| Joyce et al[17] | High dose bicalutamide (150 mg/day) | 31 | 23 | Not available |
| Scher et al[16] | High dose bicalutamide (200 mg/day) | 51 | 14 | 4.0 |
| Kassouf et al[19] | Nilutamide (200 or 300 mg/day) | 28 | 29 | 7.0 |
| Desai et al[39] | Nilutamide (150 or 300 mg/day) | 14 | 50 | 11.0 |
| Debruyne et al[36] | Cyproterone acetate (100 mg 2 times/day) | 161 | 4 | 3.6 |
| Adrenal androgen inhibitors: | | | | |
| Small et al[9] | Ketoconazole (400 mg 3 times/day) + hydrocortisone + AAWD | 128 | 27 | 8.6 |
| Harris et al[40] | Ketoconazole (200 mg 3 times/day) + hydrocortisone | 28 | 46 | 7.5 |
| Millikan et al[41] | Ketoconazole (400 mg 3 times/day) + hydrocortisone | 45 | 31 | Not available |
| Small et al[22] | Ketoconazole (400 mg 3 times/day) + hydrocortisone + AAWD) | 20 | 55 | 8.5 |
| Small et al[23] | Ketoconazole (400 mg 3 times/day) + hydrocortisone | 50 | 63 | 3.5 |
| Kruit et al[24] | Aminoglutethimide (1,000 mg 1 time/day) + hydrocortisone | 35 | 37 | 9 |
| Sartor et al[42] | Aminoglutethimide (450 mg 2 times/day) + hydrocortisone + AAWD | 29 | 48* | 4.0 |
| Alternative steroids: | | | | |
| Fossa et al[15] | Prednisone (5 mg 2 times/day) | 101 | 21 | Not available |
| Sartor et al[43] | Prednisone (10 mg 2 times/day) | 29 | 34 | 2.0 |
| Tannock et al[44] | Prednisone (7.5–10 mg/day) | 81 | 22 | 4.0 |
| Small et al[27] | Hydrocortisone (40 mg/day) | 230 | 16 | 2.3 |
| Kantoff et al[45] | Hydrocortisone (30 mg 1/daily/10 mg/nightly) | 78 | 14 | 2.3 |
| Morioka et al[46] | Dexamethasone (1.5 mg/day) | 27 | 59 | Not available |
| Saika et al[47] | Dexamethasone (1.5 mg/day) | 19 | 28 | Not available |
| Storlie et al[28] | Dexamethasone (0.75 mg bid) | 38 | 61 | Not available |
| Debruyne et al[36] | Liarozole (300 mg 2 times/day) | 160 | 20 | 4.6 |
| Estrogenic compounds: | | | | |
| Oh et al[30] | DES (3 mg) | 42 | 24 | 3.8 |
| Smith et al[29] | DES (1 mg) | 21 | 43 | Not available |
| Oh et al[30] | PC-SPES (3 caps) | 43 | 40 | Not available |
| Oh et al[48] | PC-SPES (6 caps) | 23 | 52 | 2.5 |
| Small et al[49] | PC-SPES (9 caps) | 37 | 54 | 4.0 |
| Pfeifer et al[50] | PC-SPES (9 caps) | 16 | 81 | Not available |

* Greater than 80% decrease in serum PSA.

patient to chemotherapy as opposed to further hormonal manipulations. Factors that correlate with more advanced disease, such as poor performance status, low hemoglobin and albumin, and high lactic dehydrogenase and alkaline phosphatase, have the largest impact on patient survival.[4] Another model validated the importance of these factors, in addition to highlighting the prognostic significance of primary tumor Gleason score and PSA.[5]

## CLINICAL TRIAL END POINTS

The selection of appropriate end points in prostate cancer clinical trials remains challenging. The United States FDA requires the demonstration of clinical benefit or an effect on an established surrogate for clinical benefit prior to approval of a therapeutic agent. Clinical benefit is considered to be a tangible benefit of obvious worth to the patient, such as survival prolongation, pain relief or measurable improvement in tumor related symptoms. Trial end points considered important are survival, time to progression, response rates, palliation and patient reported outcomes. A surrogate end point is defined as a measurement or sign used as a substitute for a clinically meaningful end point that measures directly how a patient feels, functions or survives.

Transcripts from the 2004 FDA consensus workshop on prostate cancer clinical trial end points were recently published.[6] Bone scan findings were a solid end point repeatedly shown to lead to a decrease in quality of life and survival. However, disadvantages using bone scan findings were interreader variability, need for bone scans to be done at the same intervals in all study arms to assure comparability, the fact that bone scan findings tend to lag behind PSA progression, heterogeneity among patients with positive bone scans and a lack of consensus on whether radiologists interpreting bone scans should be blinded to clinical data. The advantages of PSA as a potential end point are simplicity, repeatability, reproducibility and clear association with the disease time course. However, changes in PSA values may or may not reflect the effect of treatment. Therefore, PSA alone is not a valid surrogate for survival. PSA must also be viewed as a time dependent parameter rather than as a number. However, patterns of PSA change with time are complex and parameters such as PSA doubling time may not present a full picture of that complexity. Lastly although patient reported outcomes are an important part of the global assessment of treatment response, they continue to be regarded by the FDA as work in progress.

TABLE 2. *Side effects of select secondary hormonal therapies in AIPC*

| Drug/Side Effects | % Incidence |
|---|---|
| *Adrenal androgen inhibitors* | |
| Ketoconazole: | |
| Skin toxicity (sticky skin only) | About 29 |
| Skin toxicity (sticky skin, easy bruising + dryness) | About 20 |
| Increased liver enzymes | 4–10 |
| Nausea/vomiting | 10–15 |
| Gynecomastia (breast enlargement + tenderness) | About 15 |
| Fatigue | 6–10 |
| Edema | About 6 |
| Rash | About 4 |
| Anorexia | About 2 |
| Aminoglutethimide: | |
| Lethargy | About 41 |
| Skin rash | About 36 |
| Thrombocytopenia, leukopenia + anemia | About 2 |
| Megestrol acetate: | |
| Wt gain | 12–25 |
| Fluid retention | 5–20 |
| Nausea | About 7 |
| Thromboembolic events | 3–6 |
| *Estrogenic compounds* | |
| DES (3 mg): | |
| Gynecomastia | 40–55 |
| Fluid retention | 12–21 |
| Cardiovascular side effects | 7–21 |
| Thromboembolic events | 7–17 |

Investigators have most commonly used post-therapy decreases in PSA as a surrogate end point in advanced disease. Patients with AIPC treated at Memorial Sloan-Kettering Cancer Center with various therapies who had achieved a 50% or greater decrease in PSA at 12 weeks appeared to have a survival advantage over those who did not.[7] Multivariate analysis demonstrated that PSA decrease was the most significant factor influencing survival, although other factors such as tumor burden and extent of bone disease were also significant. These results were corroborated by trials using secondary hormonal therapies.[8,9]

## RATIONALE FOR SECONDARY HORMONAL THERAPY

There is currently no consensus on the most appropriate nomenclature for progressive prostate cancer.[10] In a patient with testosterone greater than 50 ng/ml and a tumor that is responsive to castrating therapies there is a general agreement that this may be labeled as hormone naive.[11] Measurable progression of disease despite castrate serum testosterone or progressive disease, as evidenced by at least 1 new lesion on bone scan or increasing PSA (minimum 5 ng/ml with 2 consecutive increases of 50%), has been labeled as AIPC, which is resistant to castration but sensitive to secondary hormonal manipulations, or HRPC, defined as resistant to all hormonal manipulations.[11] Most patients present first with increasing PSA and clinical or radiographic evidence of disease can be delayed by months or years.[6]

The biological mechanism of the failure of hormonal therapies is not completely understood but many factors are likely to contribute.[12] Throughout the progression of prostate cancer AR continues to be the primary effector of tumor growth and progression despite castrate testosterone, even in the presence of antiandrogens. Amplification of the AR gene is present in HRPC and it has been shown to correlate with increased AR protein expression.[12] AR mutations are most common in patients with progressive disease despite treatment with antiandrogen, reflecting the strong selection pressure induced by these agents.[12] A practical implication of these data is that each antiandrogen may interact uniquely with AR. Therefore, it is reasonable that a patient progressing while receiving antiandrogen may still respond to another member of this class of agents. After hormonal therapy alternative signaling mechanisms through AR maintain cellular proliferation and survival despite castrate testosterone. They consist of mechanisms that occur in a ligand dependent or a ligand independent manner. The former includes AR mutations, which lead to receptor promiscuity and activation by a range of steroid hormones, and amplification of the AR gene. The latter includes AR activation by nonclassic factors, such as certain growth factors (epidermal growth factor, insulin-like growth factor-1 and keratinocyte growth factor), receptor tyrosine kinases, activation of the AKT (protein kinase B) and mitogen-activated protein kinase pathways, recruitment of coactivators such as ARA70 and alternative signaling pathways.

The recent finding that an increase in AR expression is associated with resistance to antiandrogen therapy may provide insight into the development of new diagnostic and treatment strategies for advanced prostate cancer.[13] A provocative thought is that AR over expression may allow the continued growth of prostate cancer cells due to minute amounts of testosterone undetectable by conventional assays. Current methods for measuring total testosterone have limitations with regard to low concentrations and unresolved questions concerning the active form of the hormone. Development of a supersensitive testosterone detection assay may determine whether a castrate state has truly been achieved in patients with advanced prostate cancer.

## ANTIANDROGEN WITHDRAWAL THERAPY

Although it is less frequent than when originally described, a biochemical response can be achieved in approximately 15% to 20% of patients with AIPC on CAB upon antiandrogen therapy withdrawal.[2] This was initially described with flutamide and more recently with bicalutamide, nilutamide, megestrol acetate and DES. Generally, response is observed within 2 to 4 weeks after AAWD and the average response duration is approximately 5 months, although responses can be durable for 2 years or more. The largest prospective series showed a greater than 50% decrease in PSA in 13% of patients and objective responses in approximately 2% with AAWD therapy alone.[9]

## SECOND LINE ANTIANDROGEN THERAPY

The deferred use of antiandrogen after progression on gonadal androgen withdrawal has been shown to produce a greater than 50% decrease in PSA in 80% of those with localized disease and 54% of those with metastatic disease.[14] A phase III study of the European Organisation for Research and Treatment of Cancer Genitourinary Group indicated a 50% or greater PSA decrease with deferred flutamide in 23% of symptomatic patients with AIPC.[15] However, it remains unclear whether changes in PSA in this scenario translate into a survival benefit and whether there are differences in response to antiandrogens other than flutamide.

Of castrate patients with AIPC treated with high doses (150 to 200 mg) of bicalutamide 20% to 24% have PSA

decreases of 50% or greater with most responses seen in those who received prior flutamide therapy.[16–18] These findings can be explained by the longer half-life and increased affinity for the AR of bicalutamide. Furthermore, unlike flutamide, bicalutamide retains its antagonistic properties for the mutant AR. Similar responses to nilutamide following flutamide and bicalutamide therapy have been reported,[19] although to our knowledge no reports exist of responses to flutamide following bicalutamide or nilutamide therapy. A prospective study of nilutamide showed sustained PSA decreases of greater than 50% in 29% of patients, suggesting that this agent can be useful following prior bicalutamide therapy.[19]

Until recently antiandrogens were only used as a component of CAB but increasing evidence suggests that monotherapy with certain antiandrogens is an attractive alternative to castration based therapy.[20] The early use of antiandrogen therapy has raised concern that there may be a decreased response to subsequent hormonal manipulation. A subset of patients with evidence of disease progression from the 150 mg bicalutamide Early Prostate Cancer program received second line hormonal therapies, mostly castration based therapies, ie LHRH agonist, orchiectomy, CAB or antiandrogen alone.[21] Approximately 55% of patients had a 20% or greater PSA decrease after 3 months or greater of second line hormonal therapy.

## ADRENAL ANDROGEN INHIBITORS

Ketoconazole (200 or 400 mg 3 times daily) is an antifungal that interferes with cytochrome 3A4 and inhibits steroidogenesis in the testes and adrenal glands. In a pilot study patients with progressive disease despite CAB were treated with 400 mg ketoconazole 3 times daily and hydrocortisone simultaneous with AAWD.[22] Of the patients 55% had a greater than 50% PSA decrease with a median response duration of 8.5 months. When studied after AAWD, high dose ketoconazole resulted in a greater than 50% PSA decrease in 62.5% of patients and 48% showed a greater than 80% PSA decrease.[23] More recently Cancer and Leukemia Group B performed a randomized trial of AAWD alone or in combination with high dose ketoconazole with replacement doses of hydrocortisone.[9] Of patients undergoing flutamide withdrawal alone 11% had a PSA response compared to 27% who underwent flutamide withdrawal plus simultaneous ketoconazole ($p = 0.0002$). Objective responses were observed in 2% of patients treated with flutamide withdrawal alone compared to 20% of those treated with flutamide withdrawal plus ketoconazole ($p = 0.02$). In patients receiving deferred ketoconazole following progression after flutamide withdrawal PSA and objective responses were observed in 32% and 7%, respectively.

High dose ketoconazole is started at a dose of 200 mg 3 times daily for 1 week and then increased to 400 mg 3 times daily thereafter. Hydrocortisone is normally given at 20 mg with breakfast and 10 or 20 mg with dinner, and it should be ingested with food. The dose may need to be decreased if symptoms suggest hydrocortisone excess, ie ankle swelling or poor control of diabetes. Ketoconazole should be ingested on an empty stomach and if possible in the absence of histamine-2 blockers or antacids since increased gastric pH decreases absorption. The most common side effects are weakness or lack of strength, gastrointestinal complaints such as nausea or vomiting, hepatotoxicity, skin reactions and a potential risk of adrenal suppression. The principal side effects of ketoconazole are related to gastric irritation, leading to nausea and anorexia in at least 10% of patients. These side effects are due to mild adrenal insufficiency and any nausea or loss of appetite usually improves with time. While life threatening cortisol deficiency is uncommon, mild adrenal cortisol deficiency is common. Of all side effects liver damage may be the greatest concern. Patients on ketoconazole must have LFTs assessed monthly. Changes in LFTs are generally mild to moderate and in most cases they return to normal without intervention.

Aminoglutethimide is an adrenal steroid synthesis inhibitor that blocks adrenocorticoid synthesis by inhibiting the conversion of cholesterol to pregnenolone. A recent study showed a greater than 50% PSA decrease in 37% of patients with AIPC treated with 1,000 mg aminoglutethimide daily and 40 mg hydrocortisone daily with a median duration of response of 9 months and median survival of 23 months.[24] Aminoglutethimide causes lethargy, nausea and skin rash. Peripheral edema, hypothyroidism and abnormal LFTs have also been reported. Although aminoglutethimide has largely been replaced by ketoconazole, it remains an active available agent and is a reasonable consideration in patients requiring a secondary hormonal approach. Aminoglutethimide is started at a dose of 250 mg 3 times daily for 3 weeks and then increased to 4 times daily. Hydrocortisone is prescribed in the same manner as high dose ketoconazole.

Abiraterone acetate is an oral 17$\alpha$ hydroxylase/C17,20-lyase inhibitor developed as a mechanism based steroidal inhibitor following observations that nonsteroidal 3-pyridyl esters had improved selectivity for inhibiting testosterone synthesis.[25] A series of 3 dose escalating phase I studies was done in the United Kingdom that demonstrated the suppression of testosterone synthesis with a positive dose response correlation in castrate and noncastrate men with prostate cancer.[25] In castrate patients testosterone was further decreased by inhibiting testosterone synthesis in the adrenal glands. In noncastrate patients testosterone synthesis was inhibited in the gonads and adrenal glands. The onset of testosterone suppression was rapid and it achieved a nadir 2 to 3 days after initial dosing. Abiraterone acetate appears to be well tolerated and to our knowledge no serious side effects have been reported. Based on the mechanism of action this agent may have advantages over other antiandrogens by selectively inhibiting adrenal androgens and consequently decreasing serum and possibly intraprostatic testosterone to super castrate levels. The current data support the potential role of this agent in patients who have become refractory to LHRH agonists. To establish the optimal dose and regimen for chronic administration a phase I/II study to evaluate the safety and efficacy of abiraterone acetate in castrate patients with chemotherapy naïve AIPC is under way.

## CORTICOSTEROIDS

Glucocorticoid repletion is a standard supportive therapy in patients treated with agents that inhibit adrenal function. These agents may also have modest anticancer activity and numerous studies have added to our knowledge of their effects directly or indirectly. An early study suggested that corticosteroids are active in patients with AIPC treated with daily oral prednisone in doses of 7.5 to 10 mg.[26] After 1

month of therapy improvements in quality of life were noted in 38% of patients that were maintained a median of 4 months in 19%.

Much data on corticosteroids in prostate cancer comes from control arms of chemotherapy studies. In a study evaluating the antitumor effects of the antihelminthic agent suramin 16% of patients with AIPC treated with hydrocortisone alone had a greater than 50% decrease in PSA.[27] Similar PSA decreases were reported in 61% of patients treated with 0.75 mg dexamethasone 3 times daily.[28] Corticosteroids should be considered active hormonal agents for prostate cancer. However, there does not appear to be a superior dose or type of corticosteroid that is most effective in the absence of a randomized trial. These effects may also be short in duration with studies suggesting an approximate 4-month median duration of response in 20% to 30% of patients.[2]

## ESTROGEN BASED THERAPIES

Estrogens have long been known to have activity in the initial management of prostate cancer. DES is an inexpensive synthetic estrogen that decreases testosterone by decreasing LHRH secretion as well as directly inhibiting LH secretion by the pituitary gland. DES at a dose of 3 mg daily results in castrate testosterone in 1 to 2 weeks by the inhibition of LHRH production from the hypothalamus. Several studies have demonstrated the modest efficacy of estrogens in the context of AIPC with PSA responses of 26% to 66% at 1 to 3 mg DES.[29,30] In a recent study a 21% PSA response rate (50% or greater) was reported in which 3 mg DES daily plus 2 mg Coumadin® served as the control arm.[30] DES has been used at doses of 1 to 1.5 gm daily for 7 days, followed by weekly infusions at the same dose. Response rates have been 15% to 20% using National Prostate Cancer Project criteria to approximately 33% using PSA criteria. These data suggest that estrogen agonists have some activity in patients with progressive disease despite antiandrogens and there is not likely to be a significant dose response effect with DES. DES at a dose of 3 mg daily results in castrate testosterone in 1 to 2 weeks by the inhibition of LHRH production from the hypothalamus. DES is associated with significant cardiovascular toxicities, including myocardial infarction, stroke and pulmonary embolism, especially at moderate to high doses.[2] Anticoagulation with Coumadin® is recommended to prevent these side effects. Other common side effects of estrogen therapy are nausea, vomiting, weight gain, edema and gynecomastia. Gynecomastia may be decreased by prophylactic irradiation of the breasts.

Estrogen receptors are expressed in prostate cancer cells as well as in the stroma in androgen depleted tissues, raising the possibility that estrogen receptor is actively contributing to tumor growth and survival. Tamoxifen binds to estrogen receptors, acting as a partial agonist/antagonist. It has been associated with a response in patients with AIPC and in those who were hormone naïve. A phase II study of high dose tamoxifen (160 mg/m$^2$ daily) in patients with metastatic HRPC demonstrated a combined partial response/stable disease rate of 23%.[31] The antitumor effects of estrogen continues to be an area of investigation with mixed results seen to date in clinical trials.

The synthetic oral agent estramustine phosphate sodium is formed by the fusion of a nitrogen mustard to an estradiol moiety. It primarily produces an estrogenic and a microtubule inhibitory effect. When used as a single agent, estramustine has produced only modest objective response rates (5% to 19%).[32] However, recent in vitro and in vivo studies demonstrated synergy when estramustine was used in combination with other microtubule inhibitors, including vinca alkaloids, etoposide and taxanes. Two recent multicenter, phase III studies (TAX 327 and SWOG 9916) demonstrated a survival advantage of docetaxel based chemotherapy over mitoxantrone.[33,34] The results of these trials also bring into question the additional benefit of estramustine to docetaxel. Although no definitive comparison between the 2 studies can be made, patient characteristics and overall survival in the control groups are similar. Overall survival in the investigational arms of docetaxel and prednisone every 3 weeks, and docetaxel and estramustine suggests that the 2 are equivalent. Therefore, the additional toxicity seen with estramustine would support the use of prednisone over estramustine. Docetaxel is currently the only FDA approved regimen for metastatic HRPC. Second line hormonal therapy should not be used as an option to delay or avoid docetaxel in men with symptomatic metastatic HRPC who are otherwise candidates for cytotoxic chemotherapy. For a more detailed discussion of chemotherapy for advanced prostate cancer one can refer to a 2004 report on prostate cancer of the Prostate Cancer Foundation.[32]

PC-SPES (BotanicLabs, Brea, California) was a popular herbal combination of 8 well-defined compounds that was commercially available from 1996 to 2002.[30] Several clinical studies of PC-SPES in patients with AIPC demonstrated estrogenic effects and a greater than 50% PSA decrease in 52% to 81%. However, synthetic estrogens, DES and ethinyl estradiol were detected in various lots of PC-SPES, leading to its removal from the market.

## PROGESTINS

As with estrogens, the mechanism by which progestins inhibit tumor growth is not entirely clear. These agents have been shown to suppress gonadotropin and adrenocorticotropic hormone secretion. In addition, they may exert direct cytotoxic effects. Three progestins have been used to treat prostate cancer, namely CPA, megestrol acetate and medroxyprogesterone acetate. CPA is a steroidal antiandrogen with progestational properties, creating a feedback inhibition of pituitary LHRH release to suppress testosterone production, and direct effects on AR. Several trials of CPA have been done in AIPC and it has been shown to decrease bone pain with some improvements in performance status.[2] CPA is generally well tolerated, and edema, weight gain and shortness of breath are rarely seen. However, liver toxicity has been recognized as a complication of long-term use. CPA is not approved by the FDA for use in the United States. Megestrol acetate may contribute effects through LHRH suppression and AR blockade, and possibly through 5$\alpha$-reductase inhibition. Studies of megestrol acetate have shown a PSA response in 10% to 15% of patients with AIPC.[2,8] Several groups have evaluated medroxyprogesterone acetate in AIPC and its primary effect seems to be the relief of bone pain.[2] The major side effects of medroxyprogesterone

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