Secondary hormonal manipulations in the management of advanced prostate cancer

Uzair B. Chaudhary, MD,[1] Mohammad H. Rashid, MD,[1] Adedayo A. Onitilo, MD,[2] Nabil K. Bissada, MD[3]

[1]Department of Medicine, Division of Hematology/Oncology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA
[2]Department of Hematology/Oncology, Marshfield Clinic-Wausau Center, Wausau, Wisconsin, USA
[3]Department of Urology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

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Prostate cancer is a heterogeneous disease and clinical outcomes vary considerably after failure of primary androgen ablation. With the development of new therapeutics the management of patients with androgen independent prostate cancer has changed considerably over the last few years. Multiple secondary hormonal manipulations are available and may lead to prolonged periods of clinical response. These maneuvers include the use of oral antiandrogens, antiandrogen withdrawal, ketoconazole, aminoglutethimide, corticosteroids and use of estrogenic compounds. This article reviews the clinical activity of these agents in management of patients with advanced prostate cancer.

Key Words: prostate cancer, hormone refractory, hormone treatment, androgen deprivation, antiandrogens, steroids

Introduction

There were 679,000 new cases of prostate cancer worldwide in 2002,[1] making this the fifth most common cancer in the world and the second most common in men (11.7% of new cancer cases overall; 19% in developed countries and 5.3% in developing countries). Due to a relatively good prognosis, it is a less prominent cause of mortality with 221,000 deaths (5.8% of cancer deaths in men and 3.3% of all cancer deaths).[1] Three-quarters of all cases are in men aged 65 or more. Incidence rates are now influenced by the diagnosis of latent cancers by screening asymptomatic individuals, so that where this practice

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Address correspondence to Dr. Nabil K. Bissada, Department of Urology, UAMS, 800 Marshall Street, Little Rock, Arkansas 72202 USA

is common, the "incidence" may be very high (111.9 per 100,000 in North America; where it is now by far the most commonly diagnosed cancer in men). Incidence is high also in Northern and Western Europe and Australia/New Zealand. Mortality is affected by survival, and survival is significantly better in high-risk countries (ratio of age-standardized rates is 87% in the United States versus 45% in developing countries,[1] but much of this a consequence of more latent cancer being detected by screening procedures. In fact, the relative survival in the United States in 1995–2000 is reported to be 99%![2] As a result, mortality rates are probably a better guide to the risk of invasive prostate cancer in different populations. Mortality rates are high in the Caribbean, Southern and Central Africa, North and West Europe, Australia/New Zealand, and North and South America, and low in Asian populations and North Africa. Variations in mortality rates between China and the United States are 16-fold (almost 80-fold for incidence).[1]

Prostate cancer is the second leading cause of cancer-related death among men in the United States. It is estimated that 230,110 men will be diagnosed with prostate cancer and 29,900 fatalities will occur in 2004;[1] for Canada in 2004, an estimated 20,100 men will be diagnosed with prostate cancer and 4,200 will die of it.[3] Deprivation of androgenic steroids is the primary therapeutic approach for advanced prostate cancer providing disease response in over 90% of individuals. However in spite of the good initial response to primary androgen blockade almost all cancers eventually become refractory to hormonal treatment. It is recognized that androgen independent prostate cancer is a heterogeneous disease and some patients may respond to alternate hormonal maneuvers despite castrate levels of testosterone. Secondary hormonal maneuvers can be extremely helpful in patients with low symptomatic disease burden given relatively low toxicity profile and good bioavailability. In this paper we review the opportunities and challenges with such maneuvers.

Androgen and prostate cancer

The testes are the major source of androgens in males. The adrenal glands produce hormone precursors that are enzymatically converted to testosterone and dihydrotestosterone in prostatic and peripheral tissues.[4] Androgen production from testes can be terminated by orchiectomy or through inhibition of the pituitary production of luteinizing hormone (LH) and follicle stimulating hormone (FSH) by luteinizing hormone-releasing hormone (LHRH) agonists or antagonists,[5-7] known as "primary androgen blockade". The adrenal production of androgens is not suppressed by attenuation of LH and FSH levels, therefore further antiandrogen effect is attained by adding antiandrogen to the LH-FSH inhibition,[8-10] known as "complete androgen blockade" (CAB). Non-steroidal antiandrogen drugs such as flutamide, nilutamide and bicalutamide block binding of dihydrotestosterone (DHT) to androgen receptor (AR). The steroidal antiandrogens like cyproterone and megestrol in addition to blocking DHT-AR interaction also inhibit gonadotropin secretion with resultant reduction in LH, DHT and estrogen. The testicles produce 90% to 95% of the male hormones and the adrenal glands produce the remaining 5% to 10%.

Definition of castrate testosterone level

Since the classical studies of Charles Huggins and his collegues[11;12] in 1941, which established that the growth of the prostate gland, as well as of prostate cancer, was regulated by androgen, androgen blockade mechanisms has played a major role in he therapy of prostate cancer. The standard treatment for advanced prostate cancer has been the elimination of testicular androgen production through oral estrogen administration, bilateral orchiectomy, and—within the past 15 years—luteinizing hormone-releasing hormone (LH-RH) agonists.

Shortly after the recognition that prostate cancer can be treated effectively with estrogens, clinicians recognized that serum testosterone monitoring was necessary to evaluate therapeutic efficacy. In the late 1960s double-isotope-derivative dilution techniques were developed[13]and became readily available in early 1970s.[14-16] These techniques, however, are no longer used due to some limitations in accuracy,[17] but serum testosterone level in men after surgical castration was reported to be 50 ng/dL or less. Radioimmunoassay and, subsequently, chemiluminescent methods have supplanted the early analytic methods because of their improved accuracy and ease of testing. With this new techniques castrate testosterone levels are defined as less than 20 ng/dl (0.7 nmol/L).[18] These new techniques are more accurate and reduced waiting time for result.[19]

Several definitions of castrate testosterone have been reported,[13-16;20;21] with values as high as 100 ng/dl.[21] Though, the often quoted 50 ng/dl or less, is based on the older double-isotope-derivative method, despite advances in methodology with more accurate lower limits of detection, the definition of testosterone levels after bilateral orchiectomy has not changed. For example the current NCCN guideline

states that "Patients who do not achieve adequate suppression of serum testosterone (less than 50 ng/mL) with medical or surgical castration can be considered for additional hormonal manipulations (with estrogen, antiandrogens, or steroids), although the clinical benefit is not clear.[22]

Prognostic models for assessment of patients with progressive androgen independent prostate cancer

Patients who have a rising PSA despite continued androgen deprivation have the following potential courses of action which include: a) Observation b) Secondary hormonal agents c) Chemotherapy and d) Clinical trials. Observation may be reasonable in patients with a low PSA level, prolonged PSA doubling time without measurable disease.[23] Prognostic models have been developed which may be helpful in deciding the potential next step. In these models performance status, hemoglobin, lactate dehydrogenase levels, alkaline phosphatase levels and Gleason grade of the primary tumor have impact on patient survival.[24;25] These prognostic models help in deciding whether a secondary hormonal agent versus chemotherapy is the next step after failure of initial androgen deprivation.

Recently chemotherapy with docetaxel in combination with prednisone and docetaxel in combination with estramustine have been shown to improve survival in patients with metastatic androgen independent prostate cancer in comparison with the older standard of mitoxantrone and prednisone.[26;27] Currently there are few data to suggest that an early more aggressive approach with chemotherapy will be advantageous as compared to sequestial use of secondary hormonal agents. A current phase III trial conducted by the Eastern Cooperative Oncology Group is comparing whether estramustine and docetaxel chemotherapy is superior to ketoconazole and hydrocortisone in patients with progressive disease after failure of initial hormonal therapy. Currently we must rely on pace and burden of disease and patient's wishes until data from clinical trials become available.

About 70% to 75% of patients with metastatic androgen independent prostate cancer do not have measurable disease so surrogate marker like PSA has become a useful tool to measure disease activity.[28;29] Evidence suggests that in patients treated with systemic chemotherapy a decline in PSA level of greater than 50% at 12 weeks is suggestive of improved survival. In a variety of clinical trials conducted at the Memorial Sloan Kettering Cancer Center patients with decline in PSA of greater than 50% had a median survival of 25 months versus 13 months in those without such response.[14] More recently data are emerging that a decline in PSA of greater than 50% is also extremely meaningful in patients being treated with a variety of secondary hormonal maneuvers.[30;31] In a recently reported trial of patients treated with anti-androgen withdrawal with or without ketoconazole showed that patients achieving a greater than 50% decline in PSA had a median survival duration of 41 months versus 13 months in patients without such a response ($p<0.0001$).[17] Based on these data PSA responses in general have been shown to be an important indicator of response to available secondary hormonal agents.

Mechanism of androgen resistance

Androgen independence is considered to be an intrinsic but dormant property of prostate cancer cells which is activated in response to androgen deprivation[32] Table 1. There are several postulated mechanisms as to how this might happen:

- Evolution of the AR to become sensitive to very

TABLE 1. **Secondary hormonal manipulations for androgen-independent prostate cancer**

Therapy	**PSA decline > 50%**
Withrdawal response	
Flutamide withdrawal[62,81,108]	15-33
Bicalutamide withdrawal[109]	29
Second antiandrogen	
Bicalutamide[50,53,110,111]	20-24
Megestrol acetate[112,113]	4-14
Adrenal androgen inhibitors	
Ketoconazole and hydrocortisone[83,84,111,114,115]	40-80
Aminoglutethimide and hydrocortisone[116]	37
Low-dose steroids[98,117,118]	18-22
Estrogenic agents	
DES[77,119,120]	26-66
PC-SPES[91;121-123]	52-81
High dose tamoxifen[124]	38
High dose estrogen[125]	35

low serum levels of androgen[33]

- Mutations of the AR leading to activation by ligands other than testosterone.[34;35] It has been shown that to a mutated receptor an antiandrogen drug may act as such an alternative ligand.[36] As we discuss below, in some patients with progressive disease while on antiandrogen, withdrawal of antiandrogen can lead to paradoxical decline in serum PSA. Mutated ARs have also been shown to function as high-affinity cortisol/cortisone receptors, resulting in cancer growth at less than physiological concentrations of the endogenous hormones.[37]
- Advanced prostate cancer cells can evolve to express certain growth factors and their receptors.[38] Growth factors such as insulin-like growth factor (IGF-1 and IGF-2), keratinocyte growth factor (KGF), and epidermal growth factor (EGF) can lead to transcription of AR reporter genes without androgen-AR interaction.[39]
- Unveiling of dormant pathways that facilitate propagation and inhibit apoptosis. For example Bcl-2 is overexpressed in androgen independent prostate cancer.[40;41]

Continuation of primary androgen blockade

In most patients prostate cancer progresses through a sequence of events where in the beginning preponderance of prostate cancers cells are androgen dependent to a stage at the end where the majority is androgen independent. It is generally assumed that in most patients at the time of overt clinical progression there are still prostate cancer cells with retained hormonal sensitivity.[42] Evidence suggests that it is necessary to maintain castrate levels of testosterone in patients who have failed androgen ablation. Prostate cancer cells probably retain some degree of sensitivity at all stages of disease. For this reason primary androgen blockade is generally continued throughout the course of disease in clinical trials. In a retrospective analysis of 341 patients treated on Eastern Cooperative Oncology Group trials comparing 55 patients (16%) who discontinued androgen deprivation to those who continued treatment demonstrates, a modest survival advantage was seen in patients who continued androgen deprivation.[43] However a Southwest Oncology group trial failed to show survival advantage with continued androgen deprivation. However the criticism to this study is that while only 32 patients or 16% had discontinuation of androgen deprivation, the median survival of all patients was very short, approximately 6 months.[44] Evidence also suggests that treatment with exogenous androgens may lead to rapidly progressive disease in patients with metastatic prostate cancer.[45] Despite the lack of prospective clinical data, the current clinical practice is to continue androgen deprivation in the face of development of androgen independent disease.

Antiandrogen modulation

Most patients with advanced prostate cancer in the United States will be treated with an antiandrogen either at the time of medical castration or after progression after testicular androgen ablation. Although the utility of combined androgen blockade remain controversial a meta-analysis demonstrated that CAB with a nonsteroidal antiandrogen improved 5-year survival by about 2% to 3%.[8]

Flutamide

Flutamide is a pure antiandrogen. It blocks both peripheral and central hypothalamic-pituitary androgen receptors leading to a simulated true androgen deficiency. Subsequently, the levels of LH and FSH increase leading to an increase in circulating testosterone levels. This can be blocked by the concomitant administration of LHRH agonist. The half-life of flutamide is about 5 hours and it is excreted through the kidneys. Gynecomastia, nausea and vomiting are common toxicities. Rare fatal hepatic dysfunction is related to accumulation of a metabolite, FLU-1, in some patients[46] and liver function test monitoring is therefore advised. Flutamide is transported by multi drug resistance protein (MRP1) which may help explain some of flutamide resistance.[47] The role of flutamide has been studied in the second line setting. In one study 201 patients who had failed primary therapy in the form of orchiectomy, DES, or an LHRH-A alone were started on flutamide. The overall response rate was 35%. The non-responders had a 17% probability of survival at 2 years; versus 87% and 67% in those patients who showed partial and stable responses respectively. From another study Fujikawa et al suggested that flutamide as second-line hormone therapy was most effective in those patients in which first-line hormone therapy had been highly effective (nadir PSA level was within normal limits after first line treatment).[48]

A randomized EORTC trial compared the efficacy of flutamide versus cyproterone acetate in 310 men with metastatic prostate cancer and favorable

prognostic factors.[49] There was no significant difference in efficacy but the side effect profile was better for cyproterone with respect to gynecomastia, diarrhea and nausea. Cyproterone is available in Canada but not in the United States.

Bicalutamide

Bicalutamide is a long acting antiandrogen with a half life of approximately 7 days. Main toxicities are gynecomastia, diarrhea, hot flashes and transient liver function abnormalities. Doses used in clinical trials range from 50 mg to 200 mg per day. In one study of 51 patients with hormone refractory prostate cancer, high dose bicalutamide (150 mg daily) had an overall 24% response rate (decline in PSA by greater than 50%). There were no responders amongst patients that had failed two or more hormonal treatments.[50] Similarly data from the SWOG 9235 study also showed that bicalutamide had a 20% biochemical response rate (decline in PSA > 50%) in patients failing first-line hormonal therapy. It is believed that bicalutamide may have an inhibitory effect on certain mutant androgen receptors that are stimulated by other antiandrogens such as flutamide.[36;51;52] In the clinical setting it has been shown that bicalutamide at high dose is mostly (albeit modestly) effective in patients with androgen independent prostate cancer who have previously progressed on long-term flutamide.[50;53] Bicalutamide therapy is associated with relative preservation of bone mineral density (BMD). In one study BMD was maintained during bicalutamide 150 mg monotherapy at week 96 in comparison to castration which was associated with a progressive loss in BMD.[54]

Nilutamide

Nilutamide has a half-life of about 56 hours. Its toxicity profile is similar to bicalutamide except there is a risk of development of night vision problems in one quarter of patients. There are also rare case reports of fulminant hepatic failure and interstitial lung disease. In general tolerance to nilutamide is related to the overall performance status.[55] In most studies the maintenance dose is 150 mg to 300 mg per day. From one study 29% of patients who had failed prior flutamide or bicalutamide had a sustained PSA response (greater than 50% decrease) beyond 3 months with use of nilutamide. Interestingly responses were more common in patients who had had a previous antiandrogen withdrawal response.[56] This later fact contrasts with expectations based on the study by Kojima et al in which prior androgen withdrawal syndrome was not found to a be predictor of subsequent anti androgen response with flutamide or bicalutamide.[57]

Changing antiandrogen to a different kind can still produce a response in many patients. From one study 40% of patients treated with second-line nonsteroidal antiandrogen therapy and 29% treated with third-line nonsteroidal antiandrogen therapy showed a positive prostate specific antigen (PSA) response after changing antiandrogen drug. There are no randomized studies confirming superiorly of antiandrogens over other forms of secondary hormonal manipulations. In one European organization of research and treatment of cancer (EORTC) study 201 men with symptomatic hormone refractory prostate cancer (HRPC) were assigned to either prednisone 5 mg four times daily or flutamide 250 mg three times daily: there were similar rates of TTP and overall survival and no difference in subjective or biochemical response.[58]

Antiandrogen withdrawal response

Exposure of prostate cancer cells to antiandrogens for a prolonged time selects for mutations in the androgen receptor that strangely enough cause the antiandrogen itself to activate the receptor. In 1993 Dupont et al reported PSA decline after withdrawal of flutamide in patients who were failing CAB.[59] Subsequent clinical trials showed that at least 20% of men with prostate cancer failing CAB have a significant decrease in serum PSA level for an average duration of 2 to 10 months after withdrawal of flutamide.[60-62] This phenomenon was originally named "flutamide withdrawal syndrome" but later clinical studies revealed that PSA decline was a general response to withdrawal of different types of antiandrogens and not just flutamide.[63-66] From one study of 70 patients the incidence of the antiandrogen withdrawal syndrome (AWS) after first, second and third line hormonal therapy was 35.8%, 8.0% and 0%, respectively.[57] In this study the efficiency of subsequent hormonal therapy was not related to the occurrence of the antiandrogen withdrawal.

The duration of these responses is usually 4 to 6 months. Antiandrogen withdrawal is now considered a mandatory hormonal maneuver in patients with progressive disease on combined androgen blockade. Minority of patients can demonstrate significant response. It is critical that clinical trials mandate antiandrogen withdrawl before starting newer agents for treatment. The underlying mechanism of antiandrogen withdrawl has not been clearly identified. Mutations in the androgen receptors

resulting in altered response to antiandrogens[67] and amplification of the wild type androgen receptor gene[68] have been suggested as possible explanations. Withdrawal response was also noted after diethylstilbestrol (DES) withdrawl. In one case report the duration of response to withdrawal of DES was more than 3 years.[69]

Estrogens

Estrogens have an inhibitory effect on testosterone via suppression of LHRH. However the entire influence of estrogens on prostate cancer is poorly understood. For example diethylstilbestrol (DES) is a synthetic estrogen that lowers serum dehydroepiandrosterone sulfate levels[70] but on the other hand has been shown to have cytotoxic effects on both hormone sensitive and hormone resistant prostate cancer.[71]

Loss of estrogen receptor beta expression has been associated with progression from normal prostate epithelium to prostate cancer.[72] Estrogen receptor beta is believed to have anti-proliferative, anti-invasive and pro-apoptotic properties.[73] Interestingly and paradoxically preliminary observations also suggest that those prostate tumors that retain ER beta expression have a poorer prognosis in regards to relapse. Data from the Veterans Administration Cooperative Urological Research Group series between 1960-1975 showed that DES was equivalent to orchiectomy in metastatic prostate cancer but with higher cardiovascular and thromboembolic complications.[74] In the same series there was equivalent effect of 1.0 or 5.0 mg/day of DES on cancer. DES (3 mg/day) was compared to flutamide (750 mg/day) in a randomized trial involving patients with metastatic prostate cancer. Patients in the DES group had significantly longer time to treatment failure (26.4 months versus 9.7 months) and longer survival than flutamide – but 33% of patients on DES developed cardiovascular or thromboembolic complications.[75] In another study by Klotz et al hypercoagulable state induced by DES (2-3 mg/day) was not preventable by low dose warfarin.[76] There are few published reports on the use of DES in the second line setting. In one study of 21 patients DES 1 mg/day was associated with a 43% PSA response rate.[77] On the plus side, rates of bone resorption and osteoporosis are considered to be less with the use of estrogen therapies.[78]

Prostate cancer cell lines that express ER beta exclusively, respond to antiestrogen drugs ICI 182,780 and tamoxifen and can be rescued from ICI 182,780 growth inhibition by treatment with ER beta-antisense oligonucleotides.[79] Tamoxifen in combination with vinblastine showed no responses.[80] More recently aromatase inhibitors have shown no activity against prostate cancer. Currently there is no defined role of antiestrogens in the management of patients with prostate cancer.

Adrenal androgen suppression

Dehydroepiandrosterone (DHEA), DHEA sulfate and androstenedione are produced in the adrenal glands through the activity of CYP17 (P450c 17). Adrenal androgens are collectively responsible for about 5%-10% of androgenic steroid activity. Patients that fail CAB might still respond to suppression of adrenal androgen production by P450 inhibitors.[81] This response maybe due to the fact that mutated androgen receptors might still be somehow responding to the adrenal androgens. Alternatively adrenal androgens may be acting via a yet unidentified parallel signaling system.

Ketoconazole

Ketoconazole is a P450 inhibitor that suppresses adrenal production of androgens but may also have direct inhibitory effects on prostate cancer cells.[82] Nausea and vomiting are common side effects but hepatotoxicity, anemia and depression can also result.

In a clinical trial of 38 patients the efficacy of ketoconazole 300 mg TID plus replacement hydrocortisone was studied in patients with hormone refractory prostate cancer.[83] Twenty one patients (55.3%) showed a decrease in PSA greater than 50% with a median duration of 6 months (range 3-48 months). Overall the median time to progression was 5 months and the median survival was 12 months (range 3-48 months). Six patients (15.8%) discontinued therapy due to intolerable side effects.

In a Cancer and Leukemia Group B (CALGB) phase III trial of 260 patients with androgen-independent prostate cancer the therapeutic effect of antiandrogen withdrawal alone was compared with simultaneous antiandrogen withdrawal and ketoconazole plus hydrocortisone therapy (ketoconazole: 400 mg TID; hydrocortisone 30 mg p.o. morning and 10 mg p.o. evening).[17] Eleven percent of patients undergoing anti-androgen withdrawal alone had a PSA response, compared to 27% of patients who underwent anti-androgen withdrawal plus ketoconazole. Objective response rates were 2% and 20% respectively. There was no difference in survival. Interestingly a rise in androgen level was noted at the time of ketoconazole failure denoting development of some escape

phenomenon. In a study of 28 patients, low dose ketoconazole (200 mg orally, three times daily) plus replacement hydrocortisone was associated with a 46% PSA response rate.[84] Median duration of PSA decrease for all responders was 30+ weeks. Four (14%) patients discontinued low dose ketoconazole due to toxicities. Sixteen patients shifted to high dose ketoconazole after disease progression of which there were no responders.

One caveat in the interpretation of most trials using ketoconazole is the simultaneous use of hydrocortisone, which is necessary to avoid symptomatic hypoadrenalism. As we discuss below, steroids can independently influence prostate cancer growth.

Aminoglutethimide

Aminoglutethimide is a P450 inhibitor (CYP 11A1) that suppresses adrenal production of androgens. It is also an aromatase inhibitor.[85] Aminoglutethimide plus flutamide was shown to reduce adrenal C-19 steroids greater than flutamide alone.[86] The dose used in most clinical trials is 250 mg orally four times daily along with replacement doses of steroids. Common toxicities are abnormal liver function tests, edema, skin rash[87] and hypothyroidism.[88] Labrie et al studied aminoglutethimide plus maintenance dose hydrocortisone in 119 patients with hormone refractory prostate cancer.[89] The overall response rate was 14.3%. The 50% probability of survival was 21.0 months for the responders and 9.2 months for the non-responders. Sartor et al studied the efficacy of aminoglutethimide in conjunction with flutamide withdrawal in patients failing flutamide, suramin and hydrocortisone. All patients were continued on hydrocortisone and non-surgically castrated patients were continued on leuprolide. Fourteen out of twenty nine patients (48%) had a PSA decline greater than 80% for 4 or more weeks. Also noted were improvements in anemia, thrombocytopenia, soft-tissue masses, bone scans, and symptoms.[90]

PC-SPES

PC-SPES is an herbal amalgamation that was found to have efficacy in the treatment of androgen dependent and androgen independent prostate cancer in a prospective trial.[91] It probably works primarily via a strong estrogenic action. However other herbs in the formula are also known to carry anticancer potential: for example Isatis contains indirubin which is active in certain kinds of leukemia[92] and Rabdosia contains oridonin and ponicidin that have antiangiogenic activity.[93] Ganoderma has been reported to reduce the growth of breast and prostate cancer cells in vitro.[94] The discovery of contaminations of undeclared prescription drugs including DES and warfarin led to the recall of this compound from the market in February 2002.

Corticosteroids

Corticosteroids reduce adrenal steroidogenesis. Other mechanisms include inhibition of hormone refractory prostate cancer (HRPC) growth by disruption of nuclear factor-kappaB - IL-6 dependent pathways.[95] As single agents corticosteroids have been shown to reduce serum PSA and improve symptoms. In general a PSA decline by greater than or equal to 50% is noticed in approximately 20% of patients taking prednisone alone (usual dose is 5 mg– 20 mg per day) with median duration of response in the range of 2-3 months.[96;97] Corticosteroids can also have significant beneficial effects on quality of life as well. Tannock et al reported on 37 patients with hormone refractory prostate cancer taking oral prednisone at 7.5 mg to 10 mg orally daily. At 1 month 38% of patients reported improvement in quality of life. This palliative effect was maintained for a median of 4 months in 19% of patients.[98] In another study 37 patients with HRPC treated with oral dexamethasone (0.5-2 mg/day),[99] 62% had a decline in serum PSA >50% and 61% had decline in bone pain. The median time to PSA progression was 9 months and patients whose PSA level declined by ≥ 50% had significantly extended survival (median 22 months).

Majority of the data on corticosteroids in hormone refractory prostate cancer come from the control arm of various phase III trials. In the Phase III Suramin trial 16% of 231 patients with androgen independent prostate cancer achieved a greater than 50% decline in PSA while on 40 mg/d of hydrocortisone. Progression occurred in 31% of these patients at week 6 and the median survival was 279 days (164 patients crossed over to suramin after experiencing disease progression).[100] In another phase III study comparing hydrocortisone with hydrocortisone and mitoxantrone the control arm with hydrocortisone showed a 22% response rate (≥50% PSA decline.)[101]

Megestrol

Megestrol is a progestin that lowers T and DHT through various mechanisms including suppression of 5 alpha reductase and blockade of LH release. In laboratory animals it has been shown to suppress

both the androgen-dependent and androgen-independent prostatic tumors.[102] The dose studied in clinical trials varies from 160 mg/day to 1000 mg/day.[103] Headache, fluid retention, allergic skin rash and GI upset are commonly reported. Thromboembolism is the major life threatening risk factor.[104] In a small series of 21 evaluable patients megestrol was studied in the second line hormonal treatment setting. There were no complete or partial responses but disease was stabilized in six patients for 6 to 12 months and there was a 40% to 50% reduction in their prostatic acid phosphatase (PAP) level.[105] Similar results were reported by Crombie et al from another study of 37 evaluable patients who received megestrol in the second line setting.[106] There was only one partial response. The effect of increasing dose was studied by Dawson et al in a randomized study of 149 patients with hormone refractory prostate cancer.[107] Comparison was made between standard (160 mg/day) and moderately high dose megestrol (640 mg/day). A greater than 50% decline in PSA occurred in 13.8% and 8.8% of patients in the low and high dose treatment arms respectively and there were no differences in the toxicity or quality-of-life outcomes between the two groups. Median survival was 11.2 and 12.1 months for the low and high dose groups respectively.

Conclusions

Androgen independent prostate cancer is a clinically heterogeneous disease and many patients retain the ability to respond to a variety of secondary hormonal agents. Antiandrogen withdrawal is now a mandatory maneuver in patients failing combined androgen blockade. Sequential use of alternate oral antiandrogens, adrenal androgen suppressive agents, estrogens and steroids may provide significant clinical benefit in many patients. Increased understanding of the molecular mechanisms leading to hormonal resistance, androgen receptor function and signaling, and secondary signaling pathways affecting prostate cancer growth will shed light in better elucidating the responses to various hormonal agents. Identifying patients who may respond to secondary hormonal maneuvers and incorporation of these agents in combination with chemotherapy and new biological therapies will continue to be an active area of research. Given the short response durations of these hormonal maneuvers developing novel treatment strategies is critical to improve management of patients with advanced prostate cancer. □

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