Hormonal Therapy for Prostate Cancer

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Updates on hormonal therapy in the treatment of prostate cancer are presented. The most common therapy is to reduce testosterone to castrate levels. A dosage of 1 mg diethylstilbestrol daily prolonged survival in patients with advanced prostate cancer. The leuteinizing hormone–releasing hormone agonists have essentially replaced surgical orchiectomy in the vast majority of clinical settings; however, a major problem with the leuteinizing hormone–releasing hormone agonists has been the surge and flare of testosterone levels. If hormonal therapy is initiated early, the risk of major complications is significantly decreased. Combined androgen blockade is better than monotherapy, although there is only a small clinical benefit. When androgen deprivation is used for a short time and the normal androgen milieu is re-established, the side effects and toxicity of androgen deprivation are decreased. The major complications of androgen deprivation include hot flushes, reduction of bone mineral density, osteoporosis, and anemia. Intermittent androgen blockade might have the same benefits of total androgen suppression with fewer side effects, increased duration of androgen dependence, and less cost. The 10 steps to take when advising patients about initiation of androgen deprivation therapy are reviewed.
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Key words: Prostate cancer • Androgen ablation • Hormonal therapy • Diethylstilbestrol • Leuteinizing hormone–releasing hormone agonists

Despite tremendous improvements in risk assessment, diagnosis, staging, and treatment of prostatic carcinoma, hormonal therapy remains a mainstay of our treatment algorithm. The section on hormonal therapy at the 16th Annual International Prostate Cancer Update began with a review by Dr. Michael K. Brawer of the entire field.

Overview

No discussion of the role of hormonal therapy can begin without saluting the work of Huggins and Hodges.[1] Their pioneering work demonstrated unequivocally that hormonal therapy, initially with estrogen treatment, resulted in significant effects, both biochemically with acid phosphatase and alkaline phosphatase as well as clinically. The dependence of transformed prostatic epithelium on androgen is unequivocal. Evidence for this exists in preclinical models, where androgen supplementation often is essential for in vitro or in vivo establishment of prostatic malignancy; indeed, it can cause certain animals to develop prostate cancer.

In the clinical situation, the importance of testosterone in the management of prostate carcinoma is so well entrenched that therapies directed at treating this malignancy on a hormonal basis need only to demonstrate achievement of castrate levels of testosterone for approval by the US Food and Drug Administration (FDA).

The effect of androgens on the prostate epithelial cell and surrounding stroma are multi-factorial. Transport of testosterone into the prostatic epithelial cell, where it is converted by 5α reductase, and subsequent stimulation of the cytoplasmic androgen receptor by the active metabolite dihydrotestosterone results in potentiation of numerous processes in the cell by increasing transcription of several genes affected by the androgen receptor. Examples include increasing angiogenesis due to upregulation of epithelial growth factor and vascular endothelial growth factor, along with increased epithelial proliferation and decreased apoptosis.

Five pivotal arenas of clinical trials have demonstrated efficacy in the treatment of advanced prostatic carcinoma with hormonal manipulation. The first comes from a meta-analysis of the Veterans Affairs Cooperative study by Byar and Corle in 1988.[2] In this study conducted among men with advanced prostate cancer (T3 or N+), survival was prolonged in those receiving 1 mg diethylstilbestrol daily compared with lower or higher dosing (Figure 1). The dosage of 1 mg is important because it was not associated with the significant cardiovascular toxicity seen with higher doses and yet did afford a high degree of castration, which was not achieved in the lower dose cohort.

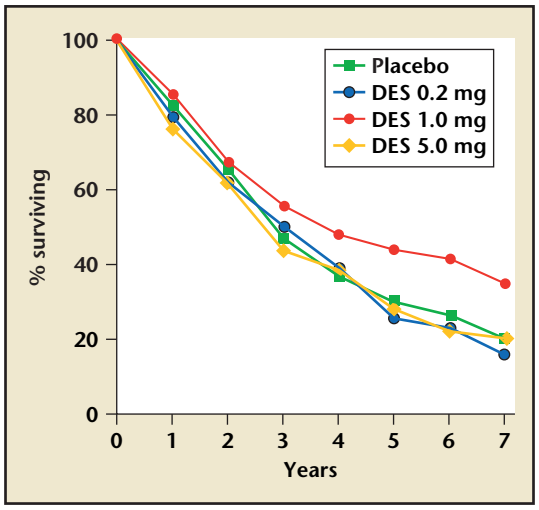


Figure 1. *Diethylstilbestrol (DES) therapy actuarial survival curves for all causes of death for patients in stages III and IV in study 2. Reprinted, with permission, from Byar and Corle.*[2]

In 1997, The Medical Research Council Prostate Cancer Working Party Investigators Group[3] published a study of advanced prostate cancer in which men were provided hormonal therapy and either surgical or medical castration at diagnosis or at progression. For all meaningful parameters, including all-cause mortality and prostate cancer–specific death, there was a significant advantage afforded to the early treatment group (Figure 2). The risk of major complications, including pathologic fracture,

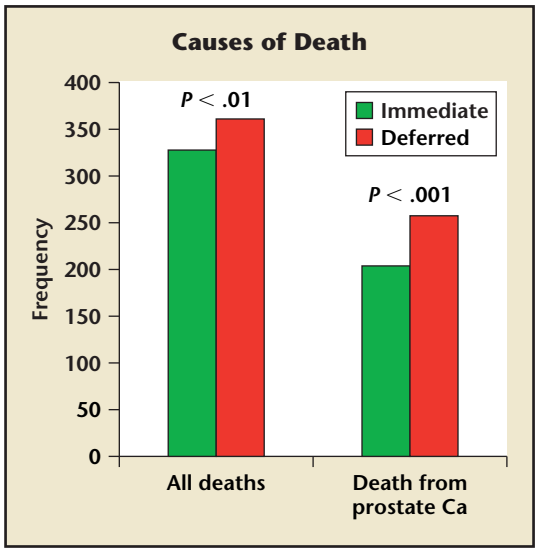


Figure 2. *Immediate versus deferred treatment for advanced prostate cancer in the Medical Research Council Trial. Data from The Medical Research Council Prostate Cancer Working Party Investigators Group.*[3]

core compression, ureteral obstruction, and extraskeletal metastasis, also was significantly decreased in the early treatment arm.

Additional studies showing the efficacy of early hormonal therapy include multiple studies in which radiation has been combined with androgen deprivation in both an adjuvant and neoadjuvant approach.[4-10] Review of these studies is reported elsewhere in this supplement and will not be described here.

Messing and associates[11] reported the use of early androgen deprivation in the face of N+ disease. Men undergoing radical prostatectomy with positive lymph nodes were randomized to receive either immediate androgen deprivation or deferred deprivation at the time of progression. These investigators demonstrated an advantage in overall survival ($P = .025$) and cause-specific survival ($P = .001$) in men who receive early androgen deprivation.

Finally, the Early Prostate Cancer trial, in which the anti-androgen bicalutamide was compared with placebo in men undergoing various forms of prostate cancer, although faulted on a number of grounds and associated with an increased all-cause mortality (perhaps related to cardiovascular toxicity), showed a delay in progression and a survival advantage in some cohorts of men with prostate cancer compared with those receiving placebo.[12-14]

Dr. Brawer then went on to describe the historical approaches to hormonal therapy, including estrogen, surgical orchiectomy, development of the leuteinizing hormone–releasing hormone (LHRH) agonists, total androgen ablation using castration with anti-androgens, and finally a brief review of the LHRH antagonists.

The LHRH agonists have essentially replaced surgical orchiectomy in the vast majority of clinical settings. More recent advances in LHRH agonists have focused on increased duration of activity. Indeed, 12-month preparations are now available. The utility of such long-acting preparations, which require a minor surgical procedure for placement, remains somewhat unclear. This is primarily because most men who are candidates for long-term androgen deprivation therapy need monitoring at much more frequent intervals than these agents potentially would require.

Few data exist regarding head-to-head comparisons between LHRH agonists. Heyns and colleagues[15] reported a comparison of triptorelin pamoate (Trelstar) versus leuprolide. Both were given in monthly preparations for 9 months. There were 137 men in the triptorelin pamoate arm and 140 in the leuprolide arm, all of whom had advanced prostate cancer. This study showed a survival advantage favoring the triptorelin pamoate arm. This intriguing finding was replicated in additional studies and suggests that all LHRH agonists might not be equal.

The major problem with the LHRH agonist has of course been the concept of surge and flare. Before the resetting of the anterior hypothalamic–pituitary–gonadal axis, stimulation of the anterior pituitary with the LHRH agonist results in an increased level of testosterone. Thompson and coworkers[16] summarized the world literature on clinical flare in a report in 1990; in a review of 9 studies, they reported a 10.9% incidence of clinical flare. Kuhn and associates[17] described, in *The New England Journal of Medicine*, that the use of an anti-androgen blocked the clinical manifestation of flare and resulted in a more prompt reduction in the serum prostate-specific antigen (PSA) level.

Crawford and associates[18] reported on National Cancer Institute (NCI) study 0036, in which men were randomized to daily leuprolide combined with either placebo or flutamide. There was a 6-month survival advantage with flutamide. The 2 curves diverged at the 3-month time-point, when a surge-induced clinical flare might have resulted in a progression of occult metastasis, resulting in progression in the LHRH-only arm (Figure 3).

The fact that the NCI 8894 study, in which men received orchiectomy alone versus orchiectomy and flutamide, did not result in statistically significant improvement in survival has been explained by many to be a result of the absence of surge and flare in men who underwent orchiectomy.

The concept of total androgen blockade has been a subject of great controversy. Perhaps the most definitive data come from the meta-analysis published by the Prostate Cancer Trialists' Collaborative Group in *The Lancet* in 2000.[19] This study demonstrated that the use of an anti-androgen in conjunction with an LHRH agonist results in an approximately 3% improvement in overall survival (Figure 4).

The development of LHRH antagonists was carried out in part to avoid surge and clinical flare. Indeed, Abarelix, the first LHRH antagonist to go through pivotal trials, achieved this important endpoint by avoiding upregulation of LH during the initial phase of administration. Unfortunately, toxicity associated with this agent has resulted in its no longer being marketed in the United States.

The clinician must then weigh the advantages of adding an anti-androgen to LHRH agonist therapy against the costs—both financial and in terms of toxicity—associated with same. In some patients, the risk–benefit ratio favors total androgen blockade.

Combined Androgen Blockade

Nicholas Vogelzang, MD, director of the Nevada Cancer Institute, presented an in-depth review of the rationale for

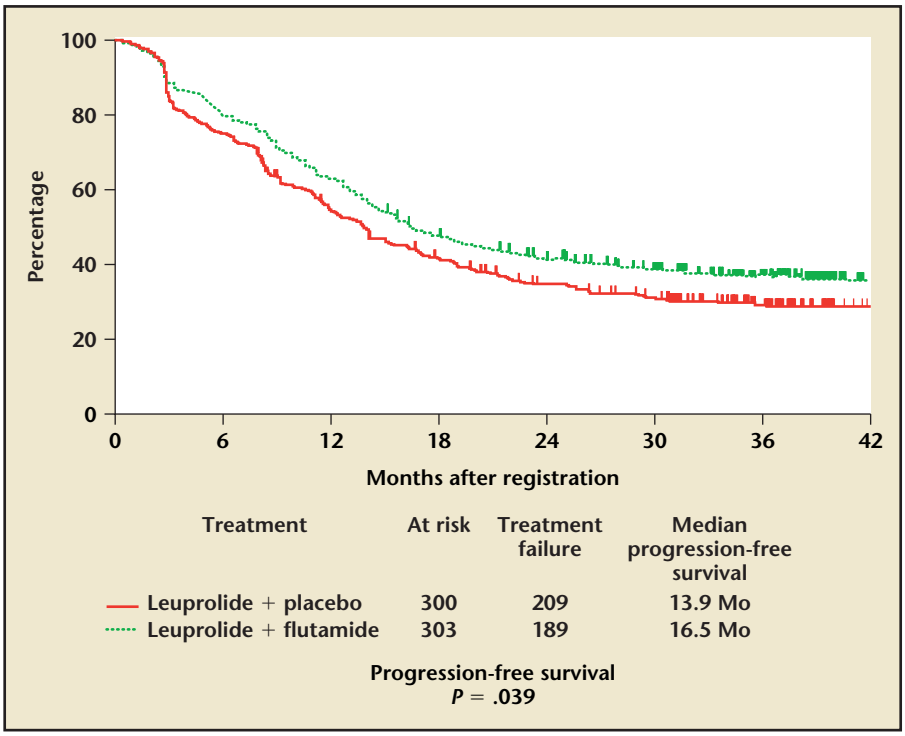
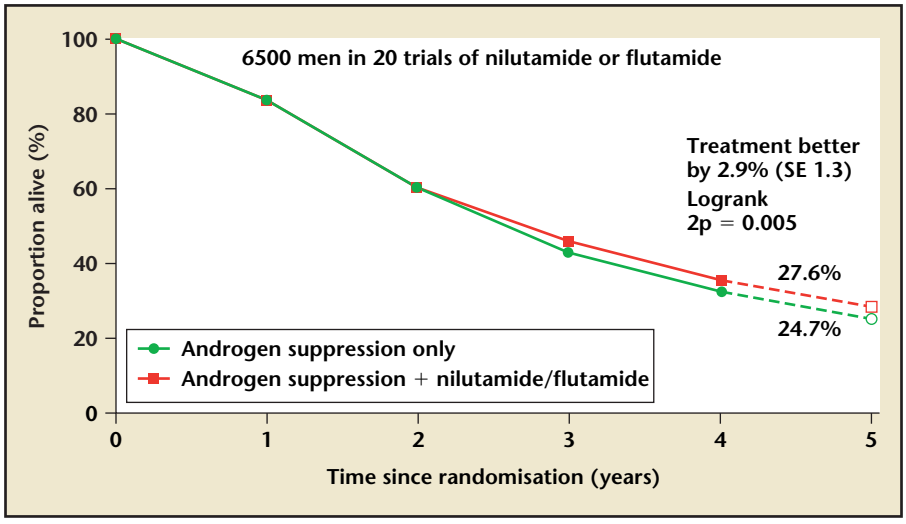


Figure 3. *Survival advantage of daily flutamide. Note how the curves diverge within just 2–3 months. They then remain parallel for 3.5 years. One wonders whether the "flare" difference in the 2 arms was the cause of the statistically significant difference between the arms. Reprinted from Crawford ED, Eisenberger MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma.* N Engl J Med. *1989;321:419-424. Copyright © 1989 Massachusetts Medical Society. All rights reserved.*

Figure 4. *Five-year survival curves for 20 trials of androgen suppression plus nilutamide or flutamide versus androgen suppression alone, and 7 trials of androgen suppression plus cyproterone acetate versus androgen suppression alone. Reprinted from The Lancet, volume 355, Maximum androgen blockade in advanced prostate cancer: an overview of the randomized trials. Prostate Cancer Trialists' Collaborative Group, pp. 1491-1498, copyright 2000, with permission from Elsevier.*



combined androgen blockade (CAB). He first provided a historical note: after the enthusiastic initial reports by Labrie and associates in Quebec of the advantage of total androgen blockade using flutamide with leuprolide therapy, reported in 1983, there were at least 27 phase III trials comparing surgical or medical castration with a variety of oral anti-androgens.

Dr. Vogelzang reported on 3 arguments in favor of CAB. First and foremost, he described *The Lancet* meta-analysis referred to above.[19] This study clearly demonstrates a survival advantage in those men receiving non-steroidal anti-androgen in conjunction with an LHRH agonist or surgical orchiectomy compared with castration alone. The meta-analysis involved 27 randomized trials involving 8275 men with primarily metastatic (88%) prostate cancer. The studies reviewed were mature—72% of patients were dead, and among them, 80% of the deaths were attributed to prostate cancer. The 5-year survival with CAB was 25.4%, compared with 23.6% in the monotherapy group. The anti-androgen cyproterone-acetate resulted in slightly unfavorable survival compared with survival with monotherapy. A subset analysis excluding the men receiving cyproterone-acetate therapy resulted in survival of 27.6% in those receiving CAB, compared with 24.7% in those without. Whether there are differences in the efficacy of the anti-androgens bicalutamide and flutamide remains controversial. At the 2004 meeting of the American Society of Clinical Oncology, Klotz and associates reported a study investigating the benefit of 50 mg bicalutamide in combination with an LHRH agonist versus castration alone. They used historical data from 2 large cohorts: the meta-analysis of the Prostate Cancer Trialists' Group described previously[19] and a multicenter study by

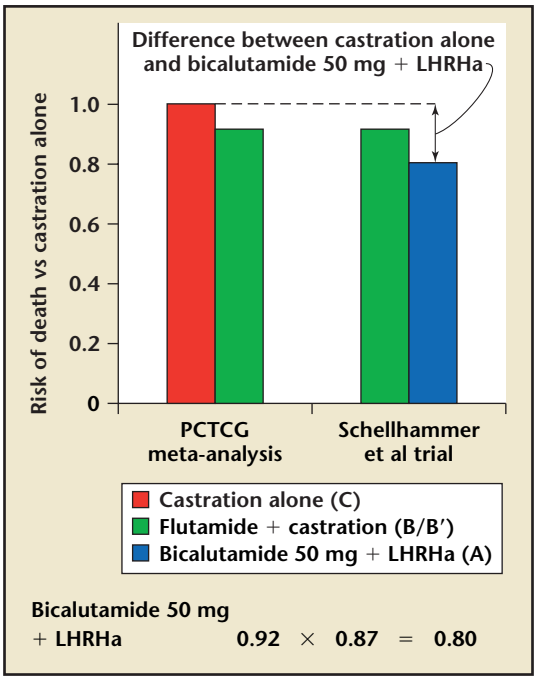


Figure 5. *Survival benefit with bicalutamide plus castration compared with flutamide plus castration. PCTCG, Prostate Cancer Trialists' Collaborative Group. Data from references 19 and 20.*

Schellhammer and colleagues, reported in 1997 in *Urology*.[20] A survival benefit was seen in those receiving bicalutamide compared with men receiving flutamide plus castration (Figure 5). The investigators concluded that the use of bicalutamide plus castration resulted in a 20% reduction in the risk of death compared with castration alone.

Stimulated by this investigation, in 2004, Akaza and colleagues[21] reported a study in which 205 Japanese men were randomized to LHRH alone versus LHRH plus bicalutamide. There was PSA normalization at 12 weeks in 80% of those receiving combination therapy, compared with 39% of those taking LHRH alone. Tumor response was 77% versus 65%, and time to failure and time to progression also favored CAB ($P = .038$ and $P = .016$, respectively).

Dr. Vogelzang then cited ongoing studies using CAB. In Radiation Therapy Oncology Group (RTOG) 9202, 1514 men with clinical stage T2c-T4 and a pre-treatment PSA concentration less than 150 mg were randomized to receive castration plus flutamide for 2 months before and during standard external beam radiation therapy as compared with the same treatment plus 24 months of long-term androgen deprivation therapy. Median follow-up was 5.9 years. There was a survival advantage in those receiving long-term androgen deprivation. Southwest Oncology Group (SWOG) 9346 is the intergroup trial investigating intermittent versus continuous androgen deprivation in men with N+ prostate cancer. After an initial period of complete androgen deprivation with goserelin and bicalutamide, men are randomized to receive either intermittent or continuous androgen deprivation therapy.

In the intergroup trial SWOG 9921, men undergoing radical prostatectomy who were deemed to be at high risk for progression are being randomized to bicalutamide plus goserelin versus bicalutamide plus goserelin along with 6 cycles of mitoxantrone and prednisone. Androgen deprivation is for 24 months. The STAMPEDE trial (Systemic Therapy in Advancing or Metastatic Prostate Cancer) is randomizing men to complete androgen blockade with or without docetaxel, zoledronate, celecoxib, or combinations. Dr. Vogelzang observed that in all of these important clinical trials combined androgen deprivation is being used as the standard.

Dr. Vogelzang concluded by stating that combined androgen blockade is better than monotherapy, although he admitted there was only a small clinical benefit. He stated that the toxicity and cost of anti-androgen might balance the benefit and thought that the paradigm of CAB is still viable but that further advances in this arena on the clinical and chemical front were important.

Intermittent Androgen Blockade

Intermittent androgen deprivation therapy offers several potential advantages in the management of men with prostatic carcinoma. Arturo Mendoza-Valdez, MD, from the Institute National, Mexico City, Mexico, provided a thorough review of this topic. Dr. Mendoza-Valdez first described the side effects of long standing androgen deprivation, including sexual dysfunction, loss of facial hair and muscle mass, anemia, osteoporosis, weight gain, mood changes, hot flushes, diarrhea, nausea, vomiting, breast tenderness, and gynecomastia. When androgen deprivation is used for a short time and the normal androgen milieu is re-established, the side effects and toxicity of androgen deprivation are decreased.

Dr. Vogelzang went on to describe the theoretical rationale based on the pioneering finding of Bruchovsky and associates in Vancouver, Canada, that there might be an increased duration of efficacy of androgen ablation with this approach. Mendoza-Valdez noted that tumor cells surviving androgen

withdrawal are forced into normal pathways of differentiation by androgen replacement, apoptotic potential might be restored, and progression to androgen deprivation might be effectively delayed. He theorized that intermittent androgen blockade might have the same benefits of total androgen suppression with fewer side effects, increased duration of androgen dependence, and less cost.

In his work with the Shionogi breast cancer model, Bruchovsky noted that time to progression with the intermittent androgen deprivation approach was 147 days versus 51 days. Klotz and associates[22] reported in *Cancer* on 19 patients undergoing intermittent androgen deprivation with cyclic administration of estrogens. The patients were evaluated for a mean of 30 months. Of the 19 patients, 12 had progression of their disease 8 months after the institution of estrogen deprivation, and all responded when subsequently treated. Sexual potency and quality of life were improved in the cohort. Numerous other studies have shown similar quality-of-life benefits with intermittent androgen deprivation therapy. Table 1 shows the clinical experience in a compilation of the literature with significant amounts of time off therapy.[22-37]

Higano and associates[39] reported in *Urology* that there was less loss of bone mineral density in patients treated with intermittent androgen suppression. The interruption of androgen blockade decreased the rate of bone loss; however, baseline levels were not achieved.

Dr. Mendoza-Valdez described a number of studies in place to evaluate the cancer control and quality-of-life benefit of intermittent versus continuous androgen deprivation. The intergroup study noted previously serves as a premier example; however, a number of other trials are currently enrolling. Survival outcome is not yet available. What has been established, however, is that the toxicity of continuous androgen deprivation is lessened and quality of life is improved when an intermittent approach is used. Relevant questions remain: Who are ideal candidates for such therapy? When should treatment be started? How long should the initial therapy be? What should be the PSA signal for re-treatment? What is the best combination? All of these questions will be answered in ongoing and future clinical trials.

For example, de Leval and colleagues[40] evaluated 68 patients, 35 of whom were treated on an intermittent basis. The mean follow-up was 30.8 months; median cycle length was 9 months with almost a 60% time off therapy. The estimated 3-year progression rate in the intermittent group was 7%, compared with 38.9% in the continuous cohort ($P = .0052$). Pether and associates[37] recently updated the Vancouver experience with intermittent androgen suppression in 102 men followed for a mean of 219 weeks—the average time off therapy was 13 months (53%) in the first cycle, compared with 8 months (45%) in the fourth. The androgen-independent progression among 29 men who progressed was 194 weeks, and death from prostate cancer occurred in 19 patients at a mean of 258 weeks. These investigators concluded that there is a trend toward extended times to progression and death in this study. Clearly we need to wait for the final results of these studies to make definitive conclusions; however, this form of therapy would seem to have a decided quality-of-life advantage and might well become the mainstay of therapy.

Table 1
Clinical Experience With Intermittent Androgen Blockade

Investigator (year)	Clinical Stage	Mean Follow-Up (mo)
Goldenberg (1995)[24]	Local + metastatic	30
Gleave (1997)[25]	Local + metastatic	46
Higano (1996)[26]	Local + metastatic	26
Oliver (1997)[27]	Local + metastatic	NA
Grossfeld (1998)[28]	Local	24
Bruchovsky (1997)[29]	Local	NA
Horwich (1998)[31]	Metastatic	NA
Kurek (1999)[32]	Local	48
Tunn (1996)[33]	Local	48
Crook (1999)[38]	Local + metastatic	33

NA, not applicable.

Targeted Systemic Therapy

Dr. Robert DiPaola, Associate Professor of Medicine at the Robert Wood Johnson Medical School, presented a thorough review of targeted systemic therapy. He introduced his discussion by noting that systemic therapy for prostate cancer is limited by hormonal and chemotherapy resistance. Expanding understanding of the molecular basis of resistance, as well as cancer progression, has resulted in

improved opportunities for targeted therapy in clinical trials. Novel therapies include treatments addressing angiogenesis, bone and stromal interactions, growth factors, metastasis microtubule formation, and tumor-specific immunity. Dr. DiPaola referred to an observation made by Hanks and colleagues,[7] who noted that the molecular mechanism of resistance increased with clinical stage. This concept in part has resulted in the belief of many that chemotherapy earlier in the course of the disease might bypass the resistance.

This is the rationale for the SWOG 9921 study, in which androgen ablation is compared with androgen ablation plus mitoxantrone and prednisone in high-risk men after radical prostatectomy. With use of a similar study design to avoid the development of resistance pathways, a planned Cancer and Leukemia Group B (CALGB) study (CALBG 90203) described by Dr. DiPaola will randomize men after radical prostatectomy with high-risk disease to radical prostatectomy alone or with neoadjuvant docetaxel (Taxotere).

With a similar design, RTOG 0521 is a phase III protocol in which men are randomized to androgen ablation and radiation therapy versus the same followed by docetaxel and prednisone in localized high-risk prostate cancer. Dr. DiPaola described several other pending studies addressing targeted approaches.

Bevacizumab is the first FDA-approved monoclonal antibody that targets vascular endothelial growth factor. The study CALGB 9040 is investigating metastatic prostate cancer, randomizing patients to a combination of dexamethasone, docetaxel, prednisone, and placebo or to the same with the bevacizumab every 21 days. The study involves 1020 patients and shows an overall survival advantage of 19 versus 24 months.

The recognition that angiogenesis and resulting neovascularity are prerequisites for progression of all human malignancies, coupled with the fact that the vascular endothelial growth factor has been established as one of the primary angiogenic promoters in prostate cancer, renders this approach to targeted therapy likely to be successful.

Atrasentan, an endothelial receptor antagonist, has been the subject of many investigations. Endothelins have been shown to be active in prostate cancer cells; they also promote neovascularization. Dr. DiPaola reported the results of 2 randomized studies in hormonal refractory prostate cancer using atrasentan. There was delay in time to progression and time to bone pain ($P < .045$ and $P < .025$, respectively); this represented a 14% decrease in progression and an 18% decrease in bone pain. This is the result of a meta-analysis, and individual studies did not show the benefit in intention-to-treat analysis. This resulted in recent failure for approval by the FDA of atrasentan and the need for further investigations.

The encouraging results of the use of docetaxel in hormone-refractory prostate cancer has resulted in a study, described by Dr. DiPaola, in which men are being randomized to docetaxel plus prednisone with or without the addition of atrasentan to determine whether there is synergy between these agents.

Dr. DiPaola noted that efforts to optimize androgen ablation therapy need to involve issues such as timing as well as the addition of novel agents. Chemotherapy and targeted systemic therapy need to be studied earlier in the course of the disease. Microtubule targeting, such as that effected by the taxanes, has been shown to be effective systemic therapy. Efforts to build on this with novel microtubule targeting agents are important areas of endeavor. Target validation of novel agents is an important aspect of development, and neoadjuvant therapy might be the optimal model for this. Dr. DiPaola concluded that a rationale exists for the assessment of vaccines in combination with androgen ablation therapy, chemotherapy, and radiation therapy.[4-9,11,41,42]

Effects of Testosterone

Paul Lange, MD, Professor and Chairman, Department of Urology at the University of Washington, reviewed the effect of testosterone treatment in prostate cancer. His presentation was certainly the most controversial and provocative of the session. He stated that testosterone might not be all bad, noting that androgen regulation of prostatic tissue is poorly understood and involves a reciprocal interaction between the epithelial and mesenchymal components. Control of epithelial proliferation is mediated at the stromal mesenchymal tissue layer, where its functional epithelial differentiation requires epithelial androgen receptor. Dysregulation of this interaction might have an effect on proliferative conditions within the prostate, including benign prostate hypertrophy and carcinoma.

Most authorities believe in at least a partially causative relationship between the presence of circling androgens and the development of prostate cancer. Clearly prostate cancer rises from androgen-dependent epithelium and is sensitive to androgen withdrawal in its early stages. Although there is no clear relationship between androgen levels and the development of prostate cancer, prostate cancer does not develop in eunuchs. Virtually all prostate cancer responds favorably to androgen deprivation. Emerging evidence also suggests that androgen stimulation might be associated with inhibiting cancer cell

growth by down-regulating growth factors. Dr. Lange observed that such a possible relationship should not be unexpected because androgen stimulation is associated with differentiation in the normal prostate.

One of the major issues Dr. Lange addressed was the use of supplemental androgen to reverse the sequelae of decreasing levels of testosterone with age (so-called andropause). This subject has been thoroughly reviewed in previous supplements to *Reviews in Urology*.[43,44] Dr. Lange noted the observation of a panel of experts convened by the Institute of Medicine, who suggested that despite the beneficial effects of supplemental testosterone in aging men, such as increased red cell mass, muscle mass, libido, feeling of well-being, and increased bone marrow, these benefits remain inconclusive.

Dr. Lange then discussed the evidence against the association of testosterone with respect to the development or exacerbation of existing prostatic carcinoma. He observed, for example, that in multiple studies in which supplemental testosterone is administered PSA does not show a significant increase. Whereas most investigators have shown a slight increase in PSA compared with baseline levels, this did not seem to increase to the level that might be associated with progression of prostatic carcinoma.

The surge response to LHRH agonist was the second point made by Dr. Lange. He noted that although there can be surge and resulting clinical evidence of progression of prostatic carcinoma (flare) in the first few weeks of LHRH therapy, in his own unpublished observation, LHRH testosterone surge results in only minimal PSA elevation.

In men treated with testosterone for andropause, there have been few case reports demonstrating the subsequent diagnosis of prostatic carcinoma. In contrast, Morgentaler and colleagues[45] reported a high incidence of occult prostatic carcinoma cases, many of which were high grade, in men who where hypogonadal. Dr. Lange thought these data suggest that testosterone replacement, at least in the short term, does not exacerbate occult prostatic carcinoma. This has been confirmed by Harman and colleagues[46] (Figure 6).

At the University of Washington, a trial of androgen-provocative testing was carried out, in which men status post–radical prostatectomy who had a high likelihood of persistent disease were given supplemental testosterone. Dr. Lange and colleagues observed no increase in serum PSA levels. Of issue was the question of whether supplemented testosterone in these mostly eugonadal men would increase the level of PSA that could unmask occult disease.

Dr. Lange then discussed the Prostate Cancer Prevention Trial, which is described elsewhere in this supplement. In this landmark study it was shown that, after 7 years, finasteride resulted in a significant decrease in the incidence of prostatic carcinoma. However, the incidence of high-grade carcinoma was increased. Please refer to the article by Dr. Kantoff elsewhere in this supplement, which raises some serious questions regarding the veracity of these data.

Finally, there are emerging reports of cases in which clinicians have

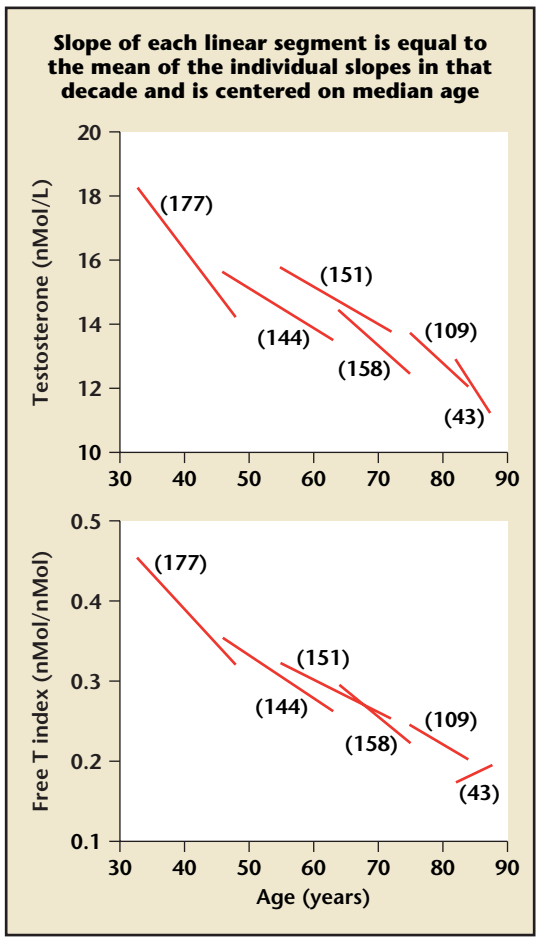


Figure 6. *Longitudinal effects of aging on date-adjusted testosterone and free testosterone (T) index. Reprinted, with permission, from Harman et al.*[46]

given testosterone to androgen-refractory patients with advanced prostate cancer with occasional promising results. Dr. Lange concluded that the advantage of testosterone replacement in men experiencing andropause should undergo more research; however, the risk with regard to prostate cancer is probably minimal. Dr. Lange concluded that testosterone replacement can be given to hypogonadal men who are without clinical evidence of prostatic carcinoma. Moreover, he stated that testosterone replacement in patients who have had radical prostatectomy and are without evidence of disease, and perhaps those who have curative therapy with other modalities and who have a low likelihood of persistent carcinoma, might only require careful monitoring. Of course the risks must be clearly delineated to the patient.[45-57]

Complications of Hormonal Therapy

E. David Crawford, MD, Professor of Surgery and Radiation Oncology, Head of the Section of Urologic Oncology at the University of Colorado, and Chairman of the 16th International Prostate Cancer Update, provided an excellent overview of complications of hormonal therapy and their treatment. He began this discussion by outlining not only the benefits but also the complications of androgen deprivation, the latter including osteoporosis, hot flushes, gastrointestinal side effects, anemia, gynecomastia, sarcopenia, central nervous system effects, change in body weight, sexual dysfunction, loss of bone density, and increased risk of bone fracture and hot flushes (Table 2).

Table 2
Complications and Rate of Occurrence of Androgen Ablation Therapy

Complication	Rate of Occurrence
Hot flushes	50%–80%
Osteoporosis	1.4%–2.6% per year
Anemia	Common
Impotence	50%–100%
Weakness	Common
Muscle wasting	Common

Dr. Crawford stated that 58% of men treated with androgen deprivation have hot flushes, which are described as sudden perceived increases in body temperature associated with reddening of the skin and profuse sweating. Rarely are there clear inciting events. The pathogenesis of hot flushes is poorly understood. Theories include a decrease in testosterone and resulting loss of regulatory feedback in the hypothalamus, and increased catecholamine release in LHRH neurons resulting in malfunction of thermal regulation. This results in heat loss and perception of a hot flush.[58]

Approximately 58% of men treated with androgen deprivation have hot flushes.

Treatment options include estrogens, megestrol acetate, clonidine, progesterone, and antidepressants, along with alternative or complementary therapies. In a study reported in *Urology*, Gerber and colleagues[59] evaluated 12 patients in an investigation of transdermal estrogen. This 4-week trial compared 2 doses of the drug. All the men had moderate-to-severe hot flushes, and 83% noted improvement in their symptoms. There was a dose effect, in that 67% of the patients on the high dose versus 25% on the low dose had moderate or major improvement in their symptom complex.

Quella and coworkers[60] studied 74 men complaining of hot flushes who were treated with megestrol acetate; 59% of the patients experienced break-through flushes; however, overall more than half the patients continued long-term utilization.

Antidepressants have been widely used for the treatment of the sequelae of androgen deprivation. No obvious agent seems to be better than others. According to Dr. Crawford, soy protein and vitamin E are the most promising. The studies have largely derived from the breast cancer literature. The mechanism of action with vitamin C is unclear; soy might work because of its known estrogenic properties. Clearly, placebo-controlled clinical trials are in order.

Hammar and colleagues[61] evaluated 7 men with advanced prostate cancer and significant hot flushes after castration. They underwent acupuncture for 10 weeks; 6 of the 7 men reported a 70% decrease in hot flushes.

Turning next to osteoporosis, Dr. Crawford noted that fully one third of hip fractures occur in men, and the major cause is hypogonadism. Although the use of the LHRH agonist for endometriosis in premenopausal women is restricted to 6 months, no such recommendations for men have been provided. There is known to be a 0.5% to 1% reduction in bone marrow density after age 35 in men. In contrast, men receiving androgen deprivation therapy lose 1.4% to 2.6% of their bone mineral density per year. With respect to age-matched controls, men receiving androgen deprivation therapy have 6.5% to 17.3% higher bone loss, and the rates of fracture are 4% to 12.5% higher.[62,63]

In a sobering trial reported in the *British Journal of Urology International*,

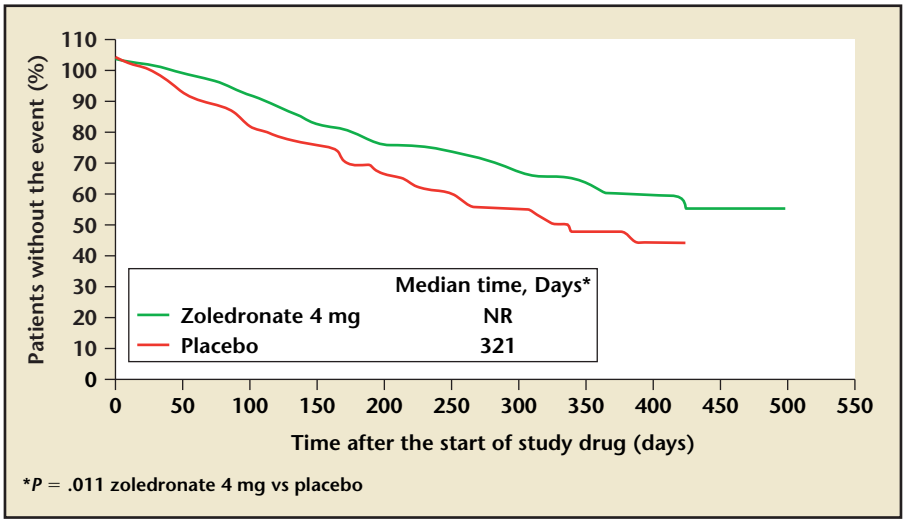


Figure 7. *Time to first skeletal-related event by treatment in a trial of zoledronate versus placebo. Data from Saad et al.*[67]

Hatano and colleagues[64] studied 218 men (mean age 77.3 years) treated for more than 6 months with an LHRH agonist for prostate cancer. They observed a 6% fracture rate, although none were at the site of metastasis. The mean time to fracture was only 28 months.

Regarding osteoporosis prevention, Dr. Crawford cited evidence involving increased physical activity, moderation of alcohol and caffeine, smoking cessation, vitamin D, and calcium replacement. He also recommended non-typical forms of androgen deprivation, such as intermittent therapy (discussed previously) and use of the bisphosphonates. Bisphosphonates result in inhibition of osteoclast formation, migration, and osteolytic activity, which results in a net increase in activity of osteoblastic and decreased activity of osteoclastic cells. In men with osteoporosis, the bisphosphonate alendronate was compared with placebo in a study by Orwoll and colleagues.[65] This study group had a significant increase in bone mineral density compared with the placebo arm, and the fracture rate was 0.8% versus 7% ($P = .02$); there was no difference in side effects between the cohorts.

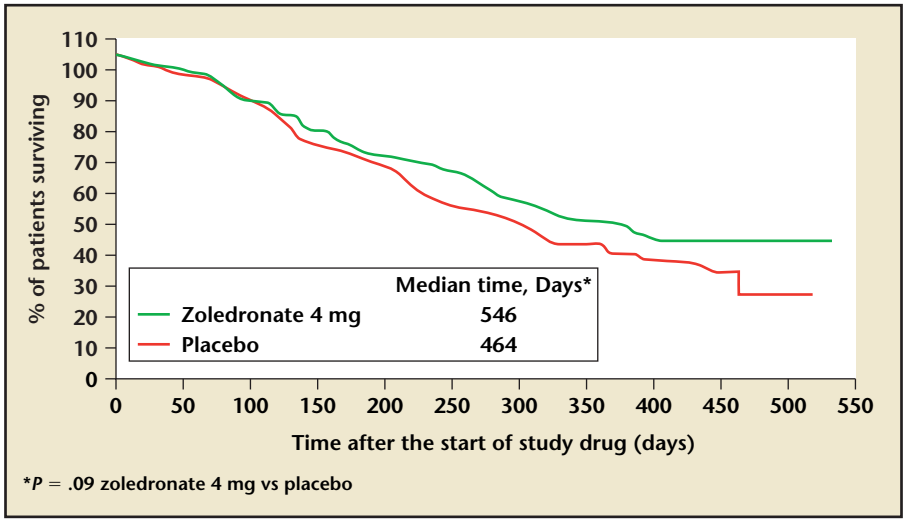
Pamidronate was studied by Smith and associates.[66] This was a study of men with advanced prostate cancer without metastasis treated with LHRH agonists alone versus LHRH agonists plus pamidronate. Patients also received bicalutamide with vitamin D and calcium. Bone mineral density was evaluated. The control group showed decreases of 3% and 2.1% in the lumbar spine and femur, respectively. There was no decrease in bone mineral density in the patients receiving pamidronate. The study was not powered to evaluate fracture.

Dr. Crawford then described his experience with zoledronate, a new class of highly potent bisphosphonates. Six hundred thirty-nine men were randomized to zoledronate with standard care versus standard care alone. Skeletal-related events included pathologic fracture, spinal cord compression, vertebral body collapse, radiation, or surgery to bone or change in anti-neoplastic therapy. Figure 7 shows the time for skeletal-related events. As can be seen, there was a significant diminution in the event rate in those men who received zoledronate. Of greater interest was a benefit (although not to the level of statistical significance) in time to death favoring the zoledronate arm, as shown in Figure 8.

Dr. Crawford concluded that the prevention of osteoporosis was important in men undergoing androgen deprivation therapy. Initial therapy with calcium supplementation to 1200 mg per day, vitamin D 600 to 800 IU, or bisphosphonate should be considered.

Dr. Crawford then addressed the issue of anemia in men with prostatic

Figure 8. *Time to death by treatment (intent-to-treat patients) in a trial of zoledronate versus placebo. Data from Saad et al.*[67]



carcinoma. This arises from the decreased red blood cell production in the setting of androgen suppression and might be exacerbated by myelosuppressive chemotherapy. Renal insufficiency decreases erythropoietin. Nutritional deficiencies might also be a factor. Fatigue, dyspnea, reduced oxygen delivery, possible reduced cognitive function, and difficulty in performance of normal activities of daily living are all stigmata of renal insufficiency. The potential of anemia should be assessed when these symptoms are present.

Treatment of anemia includes replacement of any deficiency, such as iron or folate. Recombinant human erythropoietin can be used. Dr. Crawford concluded by saying that the major complications of androgen deprivation, including hot flushes, reduction of bone mineral density, osteoporosis, and anemia, all should be looked for and properly addressed in patients undergoing this common form of prostatic cancer therapy.

Advising the Patient About Hormonal Therapy

Finally, Mark Moyad, MD, Director of Complementary and Preventive Medicine, University of Michigan, Department of Urology and Oncology, delivered an excellent discussion of the 10 steps he takes in advising patients about initiation of androgen deprivation therapy. Step 1 is to introduce patients to the common and less common side effects of androgen deprivation therapy (Table 3). Step 2 is to introduce the patient to moderate, practical, and realistic dietary and lifestyle changes that promote general health during the androgen deprivation therapy. Dr. Moyad stated that recommendations for cardiovascular well-being extrapolate well to provide benefit to patients receiving androgen deprivation therapy. Step 3 is to emphasize that when it comes to over-the-counter supplements and other alternative approaches, "less is more." He emphasized that some of these agents might have adverse effects on surgery or radiation therapy and that patients should discontinue these agents at least 1 week before definitive treatment. Step 4 is to remind patients that there might be dyslipidemia associated with androgen deprivation therapy; patients should be told, "know your lipid levels as well as your PSA."

Step 5 is to discuss possible interventions with patients who have cognitive changes, depression, erectile dysfunction, libido changes, or fatigue with androgen deprivation therapy—he emphasized that it is important to keep this simple. Step 6 is to determine with the patient the potential severity and frequency of hot flushes, and Dr. Moyad emphasized that this is best established by having patients keep a weekly diary. He

Table 3
Common and Not-So-Common Side Effects of Androgen Deprivation Therapy

- Anemia (normochromic/normocytic)
- Cholesterol/lipids
- Cognitive changes
- Depression
- Edema
- Erectile dysfunction
- Fatigue
- Glucose/insulin changes
- Hair loss/gain
- Hot flushes/chills
- Libido changes
- Muscle/joint pain
- Muscle tone reduction
- Osteoporosis
- Thyroid levels reduced
- Weight gain (abdominal)

Adapted from *Urologic Oncology,* volume 23, Moyad MA, Promoting general health during androgen deprivation therapy (ADT): a rapid 10-step review for your patients, pp. 56-64, copyright 2005, with permission from Elsevier.

Main Points

- Therapies directed at treating prostate carcinoma on a hormonal basis need only to demonstrate achievement of castrate levels of testosterone for approval by the US Food and Drug Administration.
- If hormonal therapy is initiated early, the risk of major complications is significantly decreased.
- When androgen deprivation is used for a short time and the normal androgen milieu is re-established, the side effects and toxicity of androgen deprivation are decreased.
- The major complications of androgen deprivation include hot flushes, reduction of bone mineral density, osteoporosis, and anemia.

stated that although treatment is available as described previously, most patients do not need definitive therapy, at least initially. Step 7 is to review the potential options regarding hot flushes with the patients who are significantly bothered; if there is a major impact on quality of life, intervention as described previously is useful. Step 8 is to review the risk factors of osteoporosis and screening methods for osteoporosis with the patients. Dr. Moyad noted that Medicare will soon begin covering the diagnosis and treatment of osteoporosis in men. Step 9 is to review with the patient the dietary and supplemental calcium and vitamin E sources to prevent osteoporosis. His recommendation is that screening tests for vitamin D and calcium should guide therapy. Step 10 is to review with the patient the potential drug therapies, such as bisphosphonates. He noted that most men with androgen deprivation therapy for longer than 1 year will require some form of bone marrow density protection. He stated that weight lifting was an important component of this therapy. Dr. Moyad's excellent steps are discussed in detail in his recent article.[68] ■

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