Androgen Deprivation Therapy: A Cornerstone in the Treatment of Advanced Prostate Cancer

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Decreased incidence of prostate cancer, improved therapies, and early detection have all have played some role in the decrease in prostate cancer mortality. The author discusses the development of improved methods of androgen deprivation therapy and demonstrates its significance in improved management of prostatic carcinoma.

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Key words: Hormone therapy •Androgen deprivation therapy • Mortality rates

Over the last 2 decades, there have been significant advances in the management of men with prostatic carcinoma. Concomitant with these advances is a small but real reduction in prostate cancer mortality in the United States.

There are 3 factors associated with decreasing the mortality of any disease: decreasing the incidence, improving therapy, and providing a mechanism for early detection. To decrease the incidence of prostate cancer, a number of chemopreven-

tative regimens have been applied. Most recently the Prostate Cancer Prevention Trial demonstrated a significant reduction in the incidence of prostate cancer among men treated with finasteride versus placebo for 7 years.[1] Significant controversies surround this study, particularly that the men on finasteride had more aggressive cancer detected. However, the trial undoubtedly will be the first of many focused on the incidence of prostatic carcinoma.

The biggest advance in prostate cancer has been early detection. Prostate-specific antigen (PSA) testing has revolutionized the diagnosis of prostate cancer and has become the mainstay of early detection and screening programs. Credit must also be given to the advent of transrectal ultrasound and spring-loaded biopsy devices, which provide easier sampling of prostatic tissue.

There is no question that significant strides have been made in lessening the morbidity of our most common therapeutic procedures. Anatomic radical prostatectomy (nerve sparing) has resulted in decreasing incidence of erectile dysfunction and urinary incontinence following surgery. Improvements in radiation therapy, namely, advances in brachytherapy and more directed external beam radiation therapy, have lessened complications. Additionally there has been more widespread utilization of androgen deprivation therapy in men with prostate cancer following the development of luteinizing hormone-releasing hormone (LHRH) agonist, which has been associated with improvements in overall therapy.

Despite the significant stage migration afforded by earlier detection and improvements in local therapy, the failure rate of our most widely applied approaches (radical prostatectomy and radiation therapy) is prohibitively high. Even in one of the most favorable cohorts of patients treated at the Johns Hopkins University Medical Center, an overall 15% biochemical failure rate has been reported,[2] and similar failure rates have been reported in numerous other surgical and radiation series.

Despite seemingly effective therapy and clinically localized disease, why does conventional treatment fail? First, the therapy may be unable to sterilize the tumor within the field. Although this is not the case in radical prostatectomy, this may be a factor in radiation or other nonsurgical approaches. Second, the therapy may be inadequate—the tumor may extend beyond the margins of resection in radical prostatectomy or in the radiation port. Third and most importantly, there is the likelihood of occult systemic disease. Prostate cancer cells are found in the systemic circulation and in the bone marrow in virtually all patients. Clones that can establish metastatic deposits can be missed by imaging modalities. And finally, in therapies where prostatic epithelium is left behind there may be actual recurrence or development of new malignancy.

Concomitant with advances in the management of men with prostatic carcinoma is a small but real reduction in prostate cancer mortality in the United States.

In light of these potential limitations of conventional treatment, what adjuvant therapies can applied? Options include applying more aggressive therapy, such as dose escalation in radiation, which has become more and more common. Different therapeutic approaches can be combined: for example, radiation plus surgery. The field of therapy can be expanded with wider resection in radical prostatectomy or extended field in radiation therapy. The target malignancy can be shrunk, which has been demonstrated effectively utilizing androgen deprivation therapy, but whether this results in down staging remains controversial. Finally, systemic therapy can be applied to achieve shrinkage of the known target malignancy and potentially eradicate occult metastatic disease.

It is safe to assume that decreased incidence, improved therapies, and earlier detection have all played some role in the decrease in prostate cancer mortality. In this article, the development of improved methods of androgen deprivation therapy (ADT) will be examined and its significance in improved management of prostatic carcinoma will be demonstrated.

The Role of Hormones in Prostate Cancer

There are many similarities between breast and prostate cancer, none greater than the commonality of hormonal control. In women with breast cancer, adjuvant therapy with the anti-estrogen tamoxifen demonstrated a reduced risk of recurrence of breast cancer by 47% in a meta-analysis. Moreover, mortality decreased by one fourth.[3] The success of hormonal therapy in breast cancer has resulted in numerous investigations of androgen reduction therapy in men with prostate cancer.

Circulating androgens are a prerequisite for the growth of the normal prostate and are clearly implicated in the development and expansion of epithelial cell clones that can undergo malignant transformation. Whereas the specific action of androgens in the process of carcinogenesis remains an

issue of considerable investigation, it is believed that androgens promote cellular growth and division and prostate carcinogenesis. Testosterone is a specific stimulus to the prostate.

It is recognized that the conversion of testosterone to dihydrotestosterone (DHT) results in significant stimulus amplification leading to greater adherence to the androgen receptor.[4] Conversion of testosterone to DHT occurs by the enzyme 5-alpha-reductase.[5] The requirement of DHT for prostatic development has been well established by a natural history experiment of pseudo-hermaphrodite men who have intrinsic 5-alpha-reductase deficiency. The binding of DHT to the androgen receptor results in increased transcription of androgen-regulated genes.[6,7]

Prostate carcinogenesis is undoubtedly exceedingly complex and most authorities believe it to be a multistep process.[8] A relatively small population of transformed cells may allow establishment of clones inheriting the genetic change required for the development of the malignant phenotype. Cellular proliferation stimulated by androgens allows for increased genetic instability.[9] This may allow cell clones beyond the abilities of conventional therapy to eradicate to undergo further malignant transformation and achieve a more aggressive malignant potential. Eventually this may lead to the ultimate progression of disease despite local therapy.

A number of animal models demonstrate that androgens are required to establish prostate cancer. Moreover, this occurs in a dose-dependent fashion.[10] In humans, administration of testosterone in men with established malignancy has resulted in clear clinical progression both when given therapeutically[11] and with the surge-and-flare associated with LHRH agonist administration.[12–23] These observations serve as the foundation for the interest in using androgen deprivation in conjunction with other therapies in men with high-risk prostatic carcinoma.

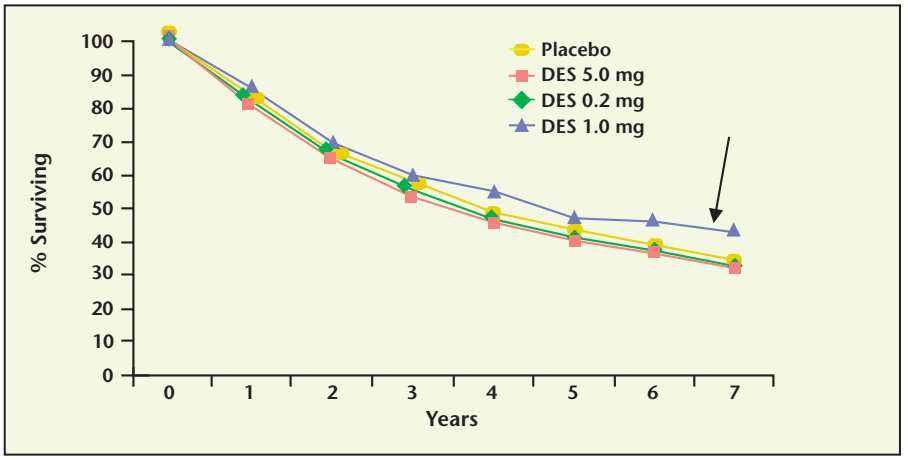

Figure 1. *Actuarial survival curves of all causes of death for patients in stages C and D2 in a Veterans Administration Cooperative Urological Reasearch Group study. Adapted with permission from Byar and Corle.[24] DES, diethylstilbestrol. Arrow indicates survival advantage at the 1.0 mg level.*

Studies Involving Androgen Deprivation Therapy as a Treatment for Prostate Cancer

A number of studies demonstrate more favorable outcomes when androgen deprivation is added as either an adjuvant or neoadjuvant therapy to conventional treatment in men with prostate cancer. Several of these studies are discussed below. Radiation therapists have conducted a number of outstanding studies utilizing androgen deprivation therapy in conjunction with conventional radiation therapy and these will be described by Dr. Roach in this issue.

The Veterans Administration Cooperative Study Group carried out a number of investigations on the use of adjuvant hormonal therapy in men with prostatic carcinoma. Byar and

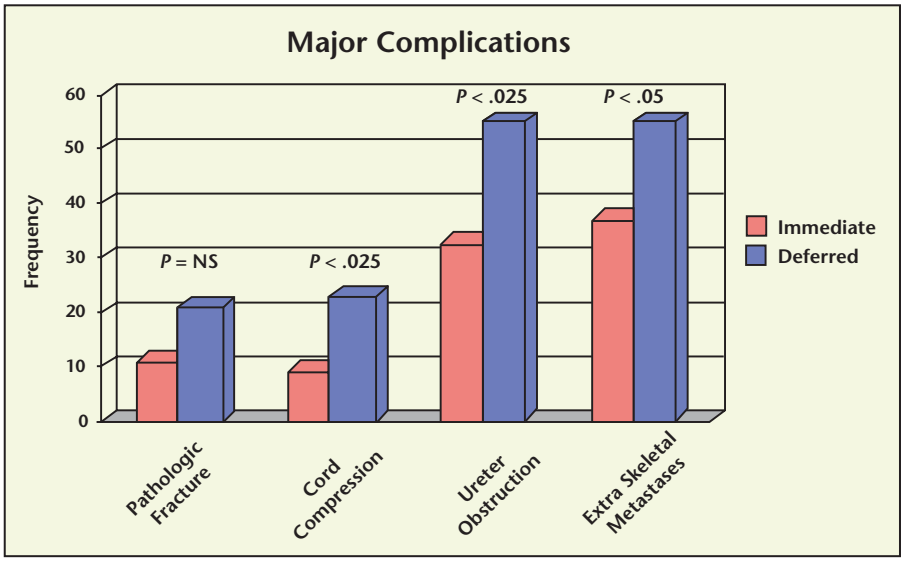

Figure 2. *Immediate versus deferred treatment for advanced prostate cancer in the Medical Research Council trial. Data from Kirk.[25] NS, not significant.*

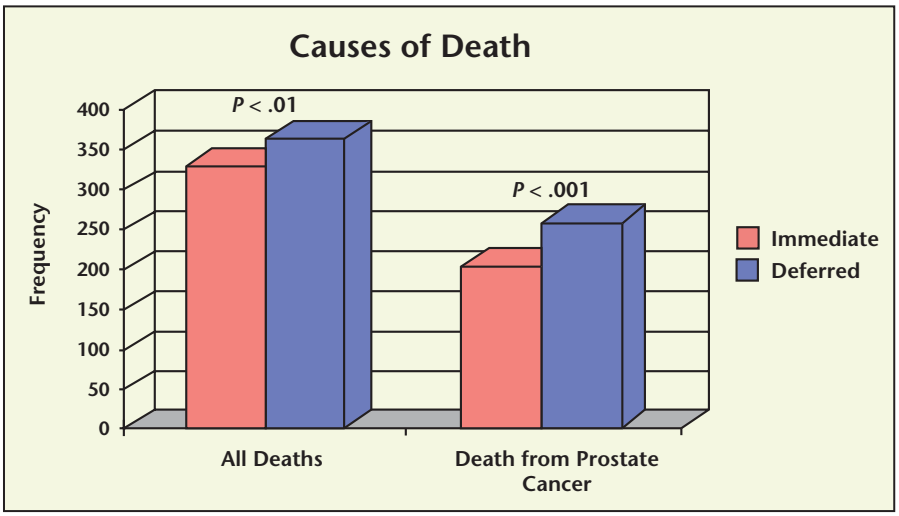

Figure 3. *Treatment for advanced prostate cancer in the Medical Research Council trial. Data from Kirk.*[25]

Corle re-examined data from one of these studies and demonstrated a survival advantage for men with advanced local prostatic carcinoma (T3) or metastatic (M+) disease. Men receiving 1 mg per day of diethylstilbestrol demonstrated a survival advantage as compared with those on placebo, or on the 0.2-mg dose (inadequate for achieving castration), or the 5-mg dose, which was associated with increased cardiovascular mortality (Figure 1).[24]

A Medical Resource Council (MRC) study[25] involved 987 men with clinical stage T3 or M+ prostate cancer, making it a similar cohort to that reported in the VA study. Men were randomized to receive immediate androgen deprivation therapy by either surgical castration or an LHRH agonist versus watchful waiting. Although this study may be faulted on a number of issues, most importantly that some of the men on watchful waiting never received androgen deprivation before death, the study clearly demonstrates, by virtually all parameters, more favorable outcomes than those receiving early androgen deprivation therapy. Figure 2 demonstrates that with respect to major complications, both statistically and clinically significant outcomes favored early androgen deprivation.

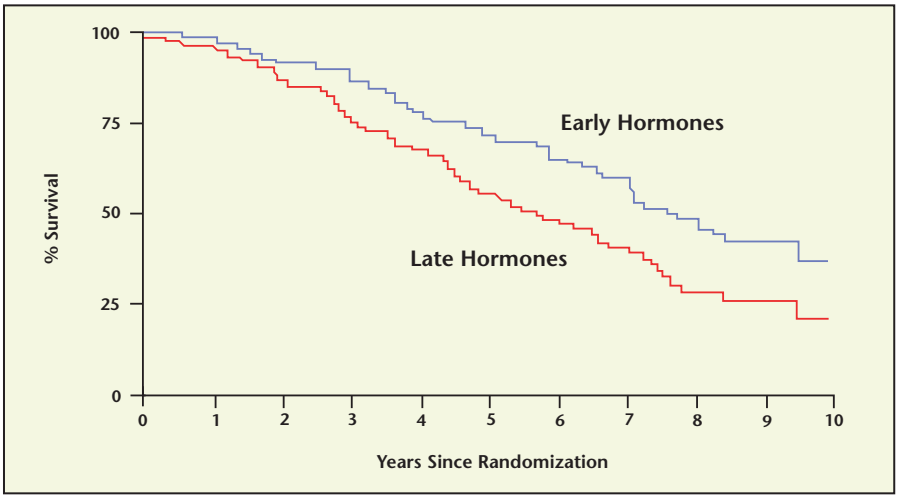

Figure 4. *Survival benefit of earlier hormone therapy in nonmetastatic disease. Adapted with permission from Kirk et al.*[25]

When examining causes of death the study demonstrated a reduction in both all-cause mortality and prostate cancer deaths related to treatment with early androgen deprivation therapy (Figure 3). Overall survival benefit in a Kaplan–Meier survival curve is depicted in Figure 4. This study confirms the initial observation noted in the VA study that the survival benefit accrues to those who receive early hormonal therapy in advanced prostate cancer. Moreover, studies with adjuvant and neoadjuvant hormone therapy in men treated with external beam radiation therapy have further supported the contention that men with advanced prostate cancer benefit from androgen deprivation.[25]

In 1999, the Eastern Cooperative Oncology Group reported results of a study comparing immediate hormonal therapy to observation in men undergoing radical prostatectomy where pelvic lymph node metastases were detected.[26] In this investigation, 98 men were randomized to receive hormonal therapy with goserelin or orchidectomy versus observation until evidence of disease progression. This study demonstrated a statistically significant all-cause survival advantage and prostate cancer–specific survival advantage. Favoring early hormonal therapy at a median follow-up of 10 years, 72.4% of patients were alive who received the androgen deprivation compared with 49% of those on observation. Cause-specific survival was 87.2% in patients receiving early hormonal therapy versus 56.9% in the comparison group (Figure 5).

Neoadjuvant hormone therapy in conjunction with radical prostatectomy (although initially believed to be encouraging) has fallen into disfavor. Despite gland and tumor volume

reduction and improved clinical and pathologic stage, as well as decreased margin positivity rates,[27] biochemical failure has not improved.[28] The discrepancy between the radical prostatectomy experience and radiation therapy remains controversial. It may be that androgen deprivation acts in a more synergistic fashion in association with radiation therapy. Alternatively, longer follow-up may be needed in the radical prostatectomy cohort in part because there may be more favorable pathologic considerations with respect to malignant potential in men undergoing surgery. Studies are ongoing with longer androgen deprivation prior to radical prostatectomy.[29,30]

It was the success of the antiandrogen program with tamoxifen in conjunction with the improved outcomes of men receiving hormonal therapy as an adjunct to radical prostatectomy that led to the bicalutamide early prostate cancer program, the largest prostate cancer trial ever conducted. Patients with prostate cancer undergoing a variety of therapeutic approaches were randomized to receive 150 mg bicalutamide qid versus placebo. The 3 major treatment groups included men undergoing radical prostatectomy, radiation therapy, or watchful waiting. Patients were enrolled with either localized or locally advanced disease. The studies were conducted throughout the world: 8113 men were randomized to a 3-year treatment regimen in the North American study and to a 5-year treatment regimen in the 2 others. Fifty-five percent of patients underwent radical prostatectomy, 17% radiation therapy, and 28% watchful waiting. Findings are shown in Figure 6. The overall findings demonstrated that in addition to standard care, bicalutamide resulted in a significant reduction in the risk of objective progression (which was defined as development of a positive bone scan or other imaging modalities, or death) of 9% versus 13.8% ($P < .0001$).[31,32]

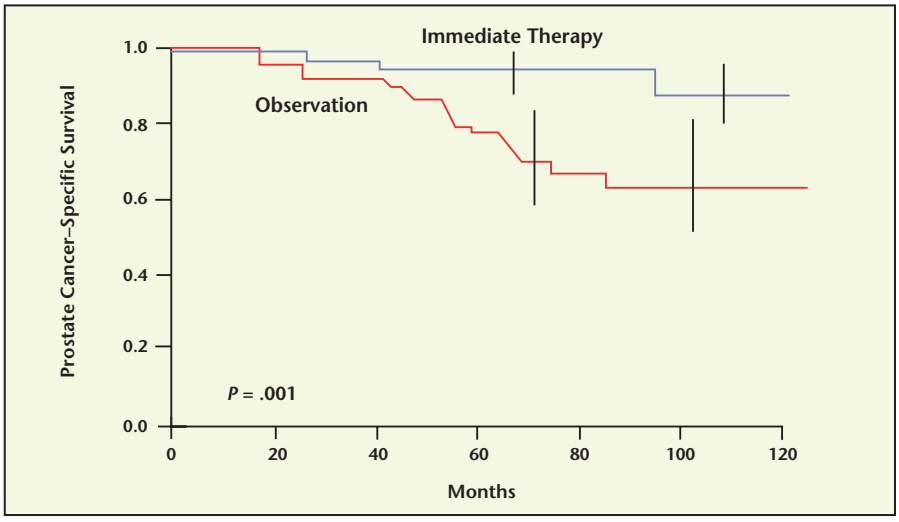

Figure 5. *Hormonal therapy versus observation after surgery for node-positive prostate cancer. Adapted with permission from Messing et al.*[26]

Patients who received bicalutamide with a worse prognosis had more significant reduction in objective progression. There was a 59% reduction relative to placebo in the PSA doubling time in patients receiving bicalutamide. PSA doubling time has recently been demonstrated[33] as an important predictor of prostate cancer death. No difference in all-cause or prostate cancer–related death was observed at the time of the first report. Recently there has been concern over increased non-prostate cancer–related death in men receiving bicalutamide, which has rendered this therapeutic approach

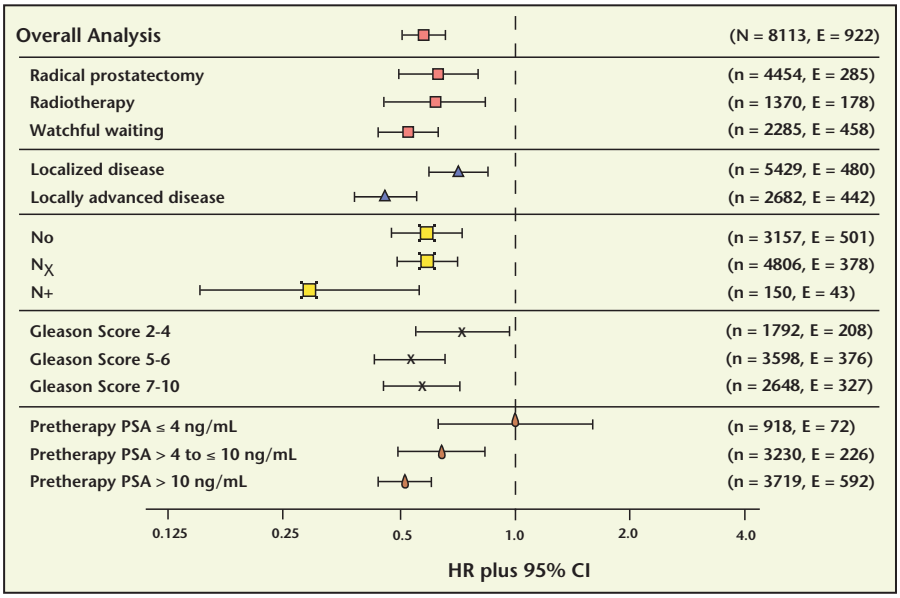

Figure 6. *The overall findings of the Bicalutamide Early Prostate Cancer Program demonstrate that in addition to standard care, bicalutamide resulted in a significant reduction in the risk of objective progression. PSA, prostate-specific antigen; HR, hazard ratio; E, events; CI, confidence interval. Reproduced with permission from See.*[32]

unfavorable by most clinicians. Further follow-up and clarification of this is required. The bicalutamide early prostate cancer program has been the subject of a recent *Reviews in Urology* supplement.[34]

In the considerably more favorable cohort of men who had radical prostatectomy in this trial, bicalutamide reduced the risk of objective progression 37% (5.1% progression rate) versus placebo (7.7% progression rate).[35] Overall, the study demonstrated that those patients at higher risk for progression due to Gleason score, pretherapy PSA level, and postprostatectomy PSA level received the greatest benefit from bicalutamide.[32]

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Future Directions

It is disheartening to note that despite significant improvements in early detection, the 2 most widespread approaches to therapy with curative intent, radical prostatectomy and radiation therapy, have significant rates of failure. Therapeutic firepower needs to be increased without increasing morbidity. Androgen deprivation therapy has been demonstrated to be effective in this regard in a variety of clinical situations. Both in a neoadjuvant and adjuvant setting, early androgen deprivation in men with more aggressive prostate cancer may indeed expand the cure rate of conventional therapy. Additional studies in a variety of settings and long-term follow-up are required to definitively assess the adequacy of these approaches and potential complications. However, androgen deprivation should be considered as part of the therapeutic approach in men with high-risk prostate cancer. ■

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Main Points

- There are three factors associated with decreasing the mortality of any disease: decreasing the incidence, improving therapy, and providing a mechanism for early detection.
- The success of hormonal therapy in breast cancer has resulted in numerous investigations of androgen reduction therapy in men with prostate cancer.
- A number of studies demonstrate more favorable outcomes when androgen deprivation is added as either an adjuvant or neoadjuvant therapy to conventional treatment in men with prostate cancer.
- Both in a neoadjuvant and adjuvant setting, early androgen deprivation in men with more aggressive prostate cancer may expand the cure rate of conventional therapy.

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