Recent Advances in Hormonal Therapy for Advanced Prostate Cancer

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Hormonal treatment of advanced prostate cancer should be considered for patients who have stages C and D1 disease, a high risk of recurrence after local therapy, or prostate-specific antigen–measured recurrence after local treatment. This approach is dependent on most prostate cancer cells being androgen-dependent, but androgen-independent cells may arise after several years of hormonal therapy. Options for androgen blockade primarily include orchiectomy, luteinizing hormone–releasing agonists and antagonists, and nonsteroidal antiandrogens. There is some controversy regarding combined androgen blockade, intermittent androgen blockade, and the question of whether early androgen blockade is superior to delayed therapy. Convincing data do exist for the use of adjuvant/neoadjuvant hormonal therapy with external-beam radiation therapy. Although hormonal therapy is an important treatment modality for advanced prostate cancer, long-term treatment carries significant side effects that need to be considered.

More than 60 years have elapsed since Huggins and Hodges first recognized the hormonal dependence of prostate cancer. The mainstay of endocrine manipulation for metastatic adenocarcinoma of the prostate is either orchiectomy or medical hormone therapy. Although the traditional definition of “advanced” prostate cancer encompasses patients with widespread osteoblastic or soft-tissue metastases, this nomenclature for advanced disease should be challenged. A more contemporary definition needs to be considered in order to maximize treatment options. This would include not only stage D2 patients, but also men with stages C and D1 (T3, T4, and any T, N1) disease, a high risk of disease recurrence after local therapy, and prostate-specific antigen (PSA) recurrence after local therapy. The premise of androgen ablation relies on growth of most prostate carcinoma cells being androgen-dependent. The androgen receptor expressed by these cells binds dihydrotestosterone, which is then transported into the nucleus, leading to a cascade of events that induces cellular growth. If androgen is removed, cellular death ensues via apoptosis of the androgensensitive cells. An androgen-independent phenotype can occur by way of androgen-resistant clones that survive and proliferate, their growth being stimulated by mitogenic growth factors. The predomination of an androgen-independent phenotype can occur approximately 1 to 2 years after the initiation of androgen deprivation. Multiple strategies have been used to induce serum levels of testosterone similar to those following castration. Traditional treatment options for androgen blockade include orchiectomy, luteinizing hormone-releasing hormone (LHRH) agonists and antagonists, nonsteroidal antiandrogens, and estrogens. Estrogens are rarely used at this time, owing to their potentially lifethreatening cardiovascular toxicity and lack of availability. In the early 1980s, LHRH agonists and antiandrogens were introduced. However, controversies exist concerning the use of LHRH agonists and antiandrogens, such as the utility of combined or total androgen blockade (ie, using an LHRH agonist plus an antiandrogen or orchiectomy plus an antiandrogen), early vs delayed hormonal therapy, and intermittent vs continuous therapy. Risk of Disease Progression and Death A large percentage of men with advanced prostate cancer have nonmetastatic extracapsular disease (stage T3). These individuals are at an increased risk of dying when compared to those with localized, organ-confined disease. A great majority of men with T3 disease are otherwise healthy, with minimal comorbid factors. Most are asymptomatic but have a substantial risk of disease progression and death; therefore, they should be treated in a manner similar to men with metastatic disease. A larger subgroup of patients would then be included, that is, men with clinical T2 cancers would be pathologically upstaged to T3 disease; this is appropriate given that between 30% and 50% of patients with clinical T2 disease have pathologic T3 cancers. A dilemma might arise over patient selection for treatment, but it is hard to deny treatment to the T3 cohort, who are at a significantly increased risk of developing metastatic disease. Another subgroup of patients—those with a persistent elevation of PSA after localized treatment by external-beam radiation or radical prostatectomy—also should be considered as having advanced disease. Recurrence Modeling
Mou[6] described the use of a recurrence model for men treated after radical prostatectomy, which was based on a model by Bauer et al.[7] Recurrence modeling appears to be helpful in identifying men at a high risk of disease recurrence. The Department of Defense Center for Prostate Disease Research model included four prognostic factors-PSA, Gleason sum, pathologic stage, and race- to derive a risk of recurrence. In this study, men in the high-risk category (relative risk > 30) had a 55.5% chance of recurrence at 3 years and an 84.8% chance at 5 years.[6] When Partin et al.[8] conducted studies in patients with stage B2 disease, they identified a select group of patients with a high risk of disease recurrence after radical prostatectomy. Our own group has developed artificial neural networks, including the prostate calculator, to assist with predicting recurrence after radical prostatectomy (www.prostatecalculator.org).[9] Although no model can be 100% predictive, individuals who are at a high risk of disease recurrence may benefit from early treatment with hormone therapy. In the future, new and innovative biochemical tools (eg, proteomics, protein screening) will yield new markers that will help clinicians not only to diagnose prostate cancer but also to identify patients at risk for progression and recurrence. **Orchiectomy vs LHRH Agonists** Although orchiectomy is an excellent modality for producing castrate levels of testosterone, it is an underused form of hormonal treatment. The procedure itself is straightforward: It can be performed in an outpatient setting and it produces an immediate reduction in levels of circulating testosterone within a few hours.[10] The first Veterans Administration Cooperative Urological Research Group study in 1967 illustrated that orchiectomy was associated with a 1-year survival rate of 73% and a 5-year survival rate of 35% among stage IV patients, vs 66% and 2%, respectively, among patients receiving placebo.[11] Over a longer follow-up period, however, hormone treatment did not have an impact on the development or course of androgen-independent disease.[12] Orchiectomy did result in subjective improvement in pain symptoms and performance status, compared with placebo. Although orchiectomy and LHRH agonists have equivalent outcomes, most patients prefer LHRH agonists because of the psychological problems associated with the removal of the testicles.[13] Another issue with orchiectomy is the irreversible nature of the procedure and the fact that it can limit future therapeutic options; for example, intermittent hormonal ablation therapy, hypothesized to delay the development of the androgen-insensitive phenotype, obviously is not possible in the setting of orchiectomy. Data from the Prostate Cancer Outcomes Study provided an update on quality-of-life issues for patients receiving hormonal therapy.[14] Those who chose LHRH-agonist treatment reported more sexual dysfunction than patients who had undergone orchiectomy; both groups had equal baseline sexual function prior to treatment. Again, however, the psychological implications of loss of the testicles may lead men to continue choosing LHRH-agonist therapy over orchiectomy. **LHRH Agonists** Currently, LHRH agonists seem to be the preferred method of hormone therapy. Since Schally et al[15] identified the structure of gonadotropin-releasing hormone (GnRH) in 1971, this molecule has been of utmost importance in the treatment of prostate cancer. GnRH, also called LHRH, is released from the hypothalamus in a pulsatile fashion and exerts its effects by stimulating the anterior pituitary to synthesize and release luteinizing hormone and follicle-stimulating hormone. Luteinizing hormone attaches to receptors on the Leydig cells of the testes, promoting testosterone production. Continuous exposure to LHRH agonists eventually causes downregulation of receptors in the pituitary, inhibiting release of both follicle-stimulating hormone and luteinizing hormone and diminishing testosterone production. The main drawback of LHRH agonists is the initial hormonal flare, during which the stimulation of pituitary GnRH receptors results in an initial surge of gonadotropins (luteinizing hormone, follicle-stimulating hormone) and androgens (testosterone, dihydrotestosterone). This flare can result in an exacerbation of symptoms, including increased bone pain, urinary retention, neurologic deficits from worsening spinal cord compression, and ureteral obstruction. The two most common LHRH agonists are leuprolide (Lupron) and goserelin acetate (Zoladex). In their depot formulations, LHRH analogs are easily administered, produce castrate serum levels of testosterone within about 1 month, and are not associated with increased cardiovascular toxicity. Phase III studies of LHRH agonists vs surgical castration demonstrated no differences in survival between the two therapies.[16] Multiple trials with symptomatic stage D patients have shown improvement in or stabilization of both local disease status and overall performance status in nearly all patients treated with LHRH agonist therapy.[17,18] **LHRH Antagonists** Newer LHRH (GnRH) antagonists under study (eg, abarelix, cetrorelix [Cetrotide]) directly block the central GnRH receptors in the pituitary. This mechanism completely avoids the initial gonadotropin and androgen surges, ultimately producing immediate castration with no exacerbation of symptoms. Abarelix was compared with leuprolide acetate in a phase III randomized trial.[19] By day 15, medical castrate levels of testosterone were achieved for 75% of patients who received abarelix, compared with 10% of patients in the leuprolide group. By
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Day 29, both groups had attained similar PSA levels. In addition to their antagonistic effects on the pituitary, GnRH antagonists may exhibit direct inhibition of androgen-independent cells in the prostate.[20] GnRH agonists cause a progressive rise in follicle-stimulating hormone until it reaches baseline; this rise in follicle-stimulating hormone does not occur with GnRH antagonists. It has not been clinically established whether this follicle-stimulating hormone-mediated role prevents or delays the occurrence of hormone-refractory prostate cancer, but it offers a new possibility for treatment modalities for hormone-refractory disease. Abarelix produces a rapid and large reduction in prostate volume (30% within 2 months) in patients receiving the compound as neoadjuvant therapy prior to brachytherapy or radiotherapy. In addition, GnRH antagonists have a reversible mode of action, which makes them applicable for neoadjuvant therapy or short treatment options such as intermittent therapy. Time and experience will be required in order for clinicians to fully evaluate the benefits of GnRH antagonists vs agonists in the treatment of prostate cancer.

Nonsteroidal Antiandrogens

About 5% to 10% of androgens are synthesized by the adrenal glands, which potentially can continue to stimulate androgen-sensitive cells. The use of nonsteroidal antiandrogens (ie, bicalutamide [Casodex], nilutamide [Nilandron], flutamide), which interfere with the binding of testosterone and dihydrotestosterone to the androgen receptor, may offer an advantage over monotherapy. In a multicenter randomized trial of 486 men with metastatic prostate cancer, bicalutamide (50 mg/d) was compared with hormone ablation either by LHRH-agonist therapy or orchiectomy.[21] The overall conclusion was that 50 mg of bicalutamide was not as effective as hormonal ablation by LHRH-agonist therapy or orchiectomy. Conventional doses of antiandrogens are not sufficient to produce adequate androgen deprivation and should not be utilized as single agents for the treatment of advanced prostate cancer. Combined Androgen Blockade

Based on the facts that low levels of androgens are produced by the adrenal glands and that monotherapy (orchiectomy or LHRH-agonist treatment) results in a 90% decrease in circulating testosterone, the use of combined androgen blockade theoretically should be superior. Although this topic is controversial, there is some evidence that combination therapy improves response and survival rates. In 1989, the Southwest Oncology Group (SWOG) published the first trial showing a potential advantage of combined androgen blockade over monotherapy.[22] This randomized, double-blind, placebo-controlled study evaluated leuprolide as a single agent vs leuprolide/flutamide in 603 men with previously untreated, metastatic prostate cancer. Compared with leuprolide monotherapy, combined androgen blockade was associated with improvement in both median progression-free survival (16.5 vs 13.9 months) and median overall survival (35.6 vs 28.3 months). In addition, the use of combined androgen blockade as initial therapy decreased the flare phenomenon. Other studies seem to validate these positive findings regarding combined androgen blockade, including the National Cancer Institute (NCI) study 0036, European Organization for Research and Treatment of Cancer (EORTC) study 30853, the Canadian Anandron Study, and the Multinational Nilutamide Study, all of which showed a survival benefit of 7 to 15 months with combination hormonal therapy.[23] Not all research findings are in agreement about the value of combined androgen blockade, however. SWOG published another study (NCI Intergroup trial 0105)[24] of 1,387 patients who were randomized to orchiectomy plus flutamide or orchiectomy plus placebo. They found no survival benefit from the addition of an antiandrogen to orchiectomy. In addition, the Prostate Cancer Trialists' Cooperative Group[25] published a meta-analysis of trials using combined androgen blockade vs monotherapy. The analysis evaluated 27 trials and included 8,275 men. The 5-year survival rate for all patients receiving monotherapy was 23.6%, compared with 25.4% for combined androgen blockade; this overall survival difference was not statistically significant. Studies to date have not resulted in a consensus regarding the clinical utility of combined androgen blockade. Early vs Delayed Therapy

Another topic of debate is the timing of hormonal ablation. Does early intervention improve survival vs delayed intervention? Although the question of when to initiate therapy remains difficult, data from several studies may assist the practitioner and patient in making this decision. In 1997, the Medical Research Council (MRC)[26] of Great Britain found that early hormonal ablation may prolong survival, compared with delayed treatment. This large study, which included 938 men with locally advanced or asymptomatic metastatic prostate cancer, had well-matched treatment groups: 469 men received hormonal therapy immediately and 465 men were given hormones only when they became symptomatic. The MRC study demonstrated an increase in disease-specific and overall survival in patients treated with immediate androgen deprivation. The impact of immediate vs delayed hormonal therapy on overall mortality (including M0, MX, M1) was 62% for the immediate treatment arm and 71% for the delayed-treatment group (P = .02). In addition, men whose therapy was deferred suffered significantly more comorbid events associated with their disease. The Eastern Cooperative Oncology Group[27] examined the impact of...
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Immediate hormonal therapy on patients with node-positive disease who underwent radical prostatectomy and pelvic lymphadenectomy. The men were randomized to one of two treatment arms (immediate androgen deprivation, achieved by goserelin or orchietomy) or were followed until disease progression. After a median follow-up period of 7.1 years, prostate cancer-specific survival, progression-free survival, and overall survival were significantly better in the group receiving immediate hormone therapy than in the control group. After 10 years, the actuarial survival of patients treated with immediate therapy was approximately 80%, compared with 55% in the deferred-treatment group. Thus, although these patients were in a high-risk category owing to their node-negative disease, early androgen deprivation improved survival. Available information suggests that early androgen suppression for the treatment of advanced prostate cancer reduces disease progression and its associated complications. Early androgen suppression may provide a small but statistically significant improvement in overall survival at 10 years. Additional studies are required to evaluate more definitively the efficacy and adverse effects of early vs delayed androgen suppression in men with prostate cancer. Patients with high-risk profiles (ie, advanced disease) should have the opportunity to discuss hormone-treatment options, and treatment should be implemented if possible. **Intermittent Androgen Blockade** Intermittent androgen blockade has received close attention over the past few years. The primary driving force behind this strategy is the avoidance of potential side effects associated with long-term use of hormone therapy, but intermittent androgen blockade may also prolong the development of an androgen-independent phenotype. Klotz et al[28] published a study of 20 patients with advanced prostate cancer who were treated with intermittent androgen blockade in the form of diethylstilbestrol or flutamide. Treatment was continued until a clinical response was seen (median treatment time: 10 months), at which point therapy was discontinued and then restarted after evidence of disease recurrence. The median relapse period was 8 months after treatment interruption. After recurrence, all patients responded to reintiation of hormonal ablation. Although no large randomized clinical trial of LHRH agonists are available, animal and in vitro cell line studies suggest that intermittent androgen blockade is beneficial.[29] Currently, the Southwest Oncology Group, the National Cancer Institute of Canada, the German Cancer Society, and the South European Uro-Oncological Group are studying the effects of intermittent androgen blockade. **External-Beam Irradiation and Neoadjuvant Hormonal Ablation** Multiple studies evaluating the efficacy of adding androgen-deprivation therapy to external-beam radiation therapy have illustrated improved outcomes in patients with localized or locally advanced prostate cancer. The Radiation Therapy Oncology Group (RTOG)[30,31] evaluated androgen deprivation as adjunctive therapy following standard external-beam radiation therapy in patients with locally advanced prostate cancer. Patients with clinical stage C (T3, N0, M0) or D1 (any T, N1-3, M0) prostate cancer were randomized to radiation plus adjuvant LHRH agent therapy, which was begun immediately and continued indefinitely, or to radiation and observation, with LHRH therapy given only at the time of relapse. **RTOG 8531** In the RTOG 8531 trial, 977 patients were randomized to receive radiation only (androgen deprivation started at disease relapse) or radiation plus adjuvant goserelin.[30] The local failure rate at 8 years was 23% for the combination-therapy arm and 37% for the radiation-alone arm (P < .0001). Disease-free survival results favored the immediate-androgen-deprivation arm (P < .0001), but overall survival was not statistically different between the two groups (49% vs 47% at 8 years). Given that only one-fourth of the patients have died thus far, however, it may be too early to assess the impact of immediate LHRH therapy on overall survival, because there has been insufficient time for evidence of any survival advantage to emerge. **RTOG 8610** It is still unclear what duration of androgen-deprivation therapy is necessary for patients to obtain the maximal benefit. RTOG 8610, conducted from 1987 to 1991, randomized 471 patients with T2 to T4 tumors, with or without pelvic lymph node involvement, to receive radiation plus combined androgen blockade with goserelin and flutamide vs radiation therapy alone.[31] Analysis at 8 years demonstrated that patients treated with combination therapy had improvements in local control (12% advantage, P = .016) and disease-free survival (12% advantage, P = .004), as well as reductions in the incidence of distant metastases (11% advantage, P = .04), and disease-specific mortality (8% advantage, P = .05). **EORTC Trial** In 1997, the EORTC published a randomized, prospective trial of 415 men (< 80 years of age) with locally advanced disease and no previous treatment of prostate cancer; data from 401 of those patients were available for analysis.[32] The study, conducted from 1987 to 1995, evaluated external-beam radiation vs externalbeam radiation/goserelin. The overall 5-year survival rate for men treated with an adjuvant LHRH agonist in addition to radiotherapy was 79%, compared with 62% in the radiation-only group (P = .001). At 5 years, 85% of surviving patients in the
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combined treatment group and 48% of the group who received external-beam treatment alone were free of disease ($P < .001$). **Evaluating Studies of Adjuvant Hormonal Treatment**

The data from the aforementioned RTOG and EORTC trials strongly suggest that adjuvant hormonal treatment in patients with locally advanced prostate cancer improves both local control and survival. Further evaluation will be necessary to elucidate the optimum duration of neoadjuvant and adjuvant hormonal therapy, the value of such therapy in earlier-stage (T1c, T2) disease, and the value and duration of antiandrogens (combined androgen blockade) in this setting. All of these studies can be critically challenged because they compared radiation therapy vs radiation therapy/androgen deprivation for a significant period of time. No study had a cohort receiving androgen-deprivation monotherapy alone, however, and hormonal therapy without radiation may produce results similar to those seen with combination radiation/hormonal therapy. Furthermore, although these studies with external-beam radiation appear to be attractive, the value of neoadjuvant and adjuvant hormonal therapy in patients treated with surgery, brachytherapy, or cryotherapy remains unknown.

**Quality-of-Life Issues** Although the efficacy of hormonal ablation is becoming increasingly clear, there is concern about the unknown effects associated with years of hormonal therapy. The most common side effect is loss of libido, but several other toxicities exist, including osteopenia, hot flashes, gynecomastia, loss of cognitive function, fatigue/malaise, depression, and loss of muscle mass.[33] If severe symptoms persist, discontinuation of therapy may be warranted. A recent study by Herr and O'Sullivan[33] assessed the quality of life of asymptomatic men with nonmetastatic prostate cancer who received androgen-deprivation therapy. Of 144 men evaluated, 79 received androgen deprivation and 65 did not. Androgen deprivation consisted of orchiectomy, leuprolide alone, or leuprolide/flutamide (combined androgen blockade). Fatigue, emotional distress, decreased physical functioning, and impaired quality of life were observed among men who received androgen-deprivation therapy; however, a greater adverse effect was seen in the combined androgen blockade group. One recent concern is that long-term treatment with androgen deprivation may result in osteoporosis.[34,35] Although one study has suggested that osteoporosis does result from long-term hormonal ablation,[36] multiple groups argue that men receiving hormonal therapy do not have significantly lower bone mineral densities than age-matched controls.[37] The precise incidence of relevant bone fractures remains unclear, especially in regard to the potential of osteopenia/osteoporosis from hormonal ablation. **Conclusions** With ongoing studies, the advantages of hormonal management for advanced prostate cancer are becoming evident. The traditional definition of advanced disease should include not only those men with widely metastatic disease but also those with a significant chance of progression and risk of death from prostate cancer: patients with stages C and D1 (T3, T4, and any T, N1) disease, those at high risk of disease recurrence after local therapy, or those with PSA recurrence after local treatment. As new molecular markers are identified, and with the use of relative-risk modeling tools (eg, artificial neural networks), an increasing number of men can begin treatment before metastatic disease develops. It is hoped that earlier initiation of therapy will reduce overall morbidity and mortality for these patients, thereby allowing them to have a longer symptom-free interval and better quality of life. Surgical castration and medical management with GnRH analogs have been shown to be equally effective. Although both forms of treatment have psychological implications, ultimately the form of therapy selected will be the patient's decision. Controversy will continue regarding the clinical utility of combination hormonal therapy. Existing data do not uniformly support the value of combination therapy in improving morbidity and survival. Currently, combined androgen blockade and treatment with monotherapy seem to be equally efficacious. The optimal timing of hormonal ablation represents another area of controversy. Does early intervention prevail over delayed therapy? Evidence suggests that early androgen suppression does reduce disease progression and complications resulting from progression. When patients have high-risk profiles, clinicians should discuss the options of early hormonal intervention, and treatment should be implemented if feasible. Concern about known and unknown effects of years of hormonal therapy use, including the potential for osteoporosis, has increased interest in intermittent androgen blockade; future studies will reveal the true efficacy of this treatment modality. The role of adjuvant/neoadjuvant hormonal therapy in the setting of external-beam radiation therapy is becoming increasingly clear. Future studies will need to include a cohort with hormonal monotherapy alone, and should identify the optimal duration of neoadjuvant/adjuvant hormonal treatment. Further research will determine the most effective treatment approaches using hormonal and other therapies. The combination of chemotherapy and hormonal therapy needs to be investigated. The ultimate goal is to identify therapies that yield the greatest efficacy without seriously compromising the well-being of the patient.
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