

1

HORMONAL THERAPY FOR PROSTATE CANCER: CLINICAL AND EXPERIMENTAL EVIDENCE

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Introduction

The role and mechanism of androgen function have been studied in a variety of androgen target organs, including the prostate. As is the case with normal prostate development, the growth of prostatic neoplasms is generally dependent on androgens, especially on 5 α -dihydrotestosterone (DHT). Since 1941 when Huggins and Hodges¹ published their Nobel Prize-winning study on the effects of hormone manipulation in patients with metastatic prostate cancer (PCa), hormonal therapy remains the critical therapeutic option for advanced disease. Multiple strategies have been used to reduce serum levels of androgens or interfere with their function via the androgen receptor (AR) (Fig. 1). However, considerable uncertainty remains as to the appropriate choice/timing and actual benefits of hormonal therapy in various situations. Indeed, PCa is still the second leading cause of cancer-related death among men in the United States.² In this chapter, we systematically review clinical and experimental evidence supporting current strategies of hormonal therapy in PCa.

The AR and Androgens

The AR, a member of the nuclear receptor superfamily, functions as a ligand-inducible transcription factor that regulates the expression of target

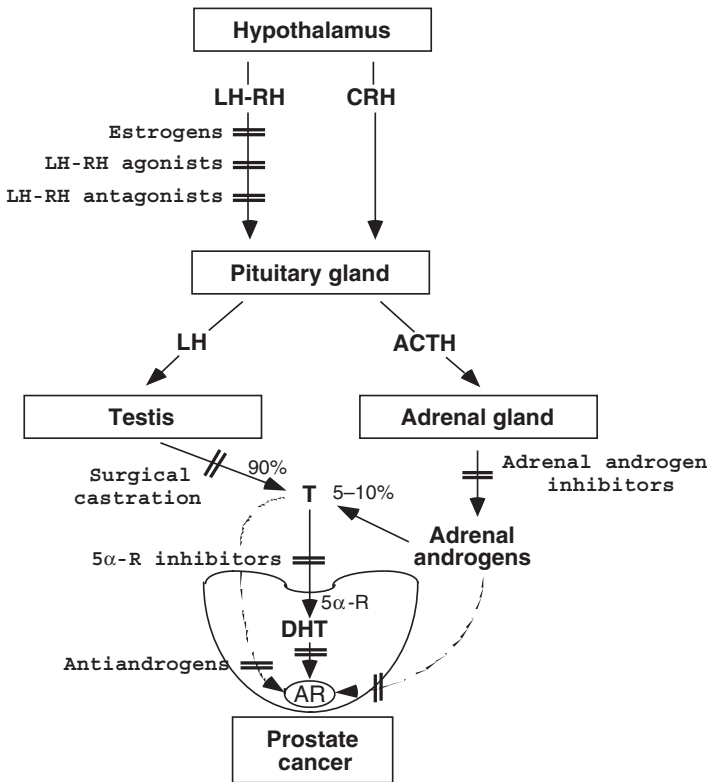


Fig. 1. Strategies for hormonal therapy. LH-RH=Luteinizing hormone-releasing hormone; CRH=corticotropin-releasing hormone; LH=luteinizing hormone; ACTH=adrenocorticotropic hormone; T=testosterone; 5 α -R=5 α -reductase; DHT=5 α -dihydrotestosterone; AR=androgen receptor.

genes in response to ligands in target cells.^{3,4} Recent studies have also revealed that the AR modulates transcription by recruitment of coregulators that influence a number of functional properties of the receptor, including ligand selectivity and DNA binding capacity (reviewed in Ref. 5).

Testosterone is secreted by Leydig cells in the testis and is the major sex hormone circulating within the blood of males. In a variety of androgen-sensitive tissues like the prostate, testosterone is irreversibly converted by 5 α -reductases to the more potent androgen, DHT.^{4,6} Upon binding of androgens, the androgen-AR complexes form homodimers, and they translocate into the nucleus and bind to androgen responsive elements

located on target genes, such as prostate-specific antigen (PSA), which is clinically used for the detection and monitoring of PCa recurrence and progression. Besides testosterone and DHT, several precursors of testosterone mainly secreted by adrenal glands, dehydroepiandrosterone (DHEA), DHEA sulfate, Δ^4 -androstenedione, and Δ^5 -androstenediol, can also stimulate the AR through their conversion to testosterone/DHT in peripheral tissues, including the prostate, or by directly binding to the AR.⁷⁻¹⁰

Strategies of Androgen Deprivation

Multiple approaches at androgen deprivation have been used for the treatment of PCa (Fig. 1). The agents and strategies used for androgen deprivation therapies are listed in Table 1.

Surgical Castration

Surgical castration by bilateral orchiectomy is the most immediate method to reduce circulating testosterone by >90% within 24 hours,¹¹ and there is no risk of a paradoxical flare of the disease. Since the 1960s, the Veterans Administration Cooperative Urological Research Group (VACURG) trials, the earliest large-scale randomized studies of hormonal therapy, demonstrated the clinical effectiveness of surgical castration.^{12,13} Compared to placebo, orchiectomy retarded cancer progression in advanced cases, but no clear survival advantage for castration over placebo was seen. Recent clinical studies (i.e. surgical vs. chemical castration) are discussed later. Although surgical castration may be underused, some studies suggest that many patients prefer this approach for the reasons of convenience and cost.¹⁴ On the other hand, other studies suggest that this treatment approach is unacceptable to many patients, causing considerable psychological problems, with irreversible impairment in libido and erectile function in most cases.^{15,16}

Medical Castration

Diethylstilbestrol (DES)

In the 1940s, the first reversible medical castration method was achieved by administration of DES, a semi-synthetic estrogen compound.¹ The

Table 1. Treatment Options as Hormonal Therapy for Prostate Cancer

Modality	Methodology	Mechanism/Action	Advantages	Disadvantages
Surgical castration	Bilateral orchiectomy	Orchiectomy, ↓T	Rapid ablation of testicular T Relatively simple procedure, lower cost	Definitive castration Associated psychological problems Irreversible loss of libido/sexual potency Reduced muscle mass/energy Hot flashes Anemia/osteoporosis Unaffected adrenal androgens
Medical castration	Estrogens (DES) LH-RH agonists (Leuprolide, Goserelin) LH-RH antagonists (Abarelix)	Suppresses LH-RH secretion, ↓LH, ↓T Direct effect via ER (?) Suppresses LH-RH secretion, ↓LH, ↓T Antagonizes LH-RH receptor, ↓LH, ↓T	Reversible castration Ablation of testicular T More acceptable than orchiectomy	Cardiovascular events (estrogens) Flare phenomenon (LH-RH agonists) Reduced muscle mass/energy Loss of libido/sexual potency Hot flashes Anemia/osteoporosis Unaffected adrenal androgens
CAB	Castration + antiandrogen	Ablation of testicular T + competitive inhibition of adrenal androgens	More effective (?)	Increased side effects Antiandrogen withdrawal response

Table 1. (Continued)

Modality	Methodology	Mechanism/Action	Advantages	Disadvantages
Antiandrogen monotherapy	Non-steroidal antiandrogens (Flutamide, Nilutamide, Bicalutamide)	Antagonizes AR in target tissues, ↑T	Competitive inhibition of testicular/adrenal androgens Retaining sexual potency Less severe side effects Oral administration only CAB effect	Gynecomastia Less effective (?)
	Steroidal antiandrogens (CPA, Megestrol acetate)	Antagonizes AR in target tissues, Suppresses LH-RH secretion, LH, ↓T	Oral administration only	Cardiovascular events Side effects due to lowering of serum T Gynecomastia
IAB	Intermittent hormonal therapy		Longer androgen-sensitive period(?) Reduced side effects/costs	Investigational May achieve continuous androgen ablation
TrAB	Intermittent CAB + 5α-R inhibitor (Finasteride, Benzoquinoline)		Superior to IAB or CAB (?)	Investigational
SAB	5α-R inhibitor + antiandrogen or LH-RH agonist		Superior to monotherapy (?)	Investigational

T = Testosterone; DES = diethylstilbestrol; LH-RH = luteinizing hormone-releasing hormone; LH = luteinizing hormone; ER = estrogen receptor; CAB = combined androgen blockade; AR = androgen receptor; CPA = cyproterone acetate; IAB = intermittent androgen blockade; TrAB = triple androgen blockade; 5α-R = 5α-reductase; SAB = sequential androgen blockade.

VACURG studies identified equivalent overall survival rate in the DES group (5 mg/day) to the orchiectomy group, but non-cancer-related deaths, most of which were cardiovascular events, were noted.^{12,13} Subsequent trials have shown that DES at 3 mg/day is equivalent to other treatment options in overall survival rates.^{17–21} However, cardiovascular toxicity with events including myocardial infarction, deep vein thrombosis, edema, and transient ischemic attack was observed in 8%–33% of patients. Gynecomastia was also significantly seen in patients with 3 mg/day DES. A low-dose of DES (1 mg/day) was also evaluated,^{13,22} but whether DES at 1 mg/day is as effective and safe as other treatment options is still controversial. After the development of luteinizing hormone-releasing hormone (LH-RH) agonists, with fewer cardiovascular events and no resulting gynecomastia, DES is now only rarely used as a first-line hormonal treatment in North America. Instead, several studies have evaluated the efficacy of DES as a salvage therapy after failure of first-line androgen deprivation. Recent studies, using 1–3 mg/day DES with or without anti-thrombotic agents, including warfarin and aspirin,^{23,24} identified response rates by PSA measurement to be 43%–79% with median durations of progression of 6–7.5 months and with 2.8%–28% cardiovascular events.

It was generally believed that the primary mechanism of action of DES was to decrease androgen levels through hypothalamic-pituitary suppression, but recent evidence indicates that the mechanism is probably more complex. Kitahara *et al.* reported stronger suppression of testosterone by DES than by surgical castration or other means of chemical castration, such as the administration of a LH-RH agonist.²⁵ The same group also suggested that DES might reduce serum DHEA sulfate.²⁶ A direct cytotoxic effect of estrogens has also been suggested in PCa *in vitro*, presumably through both estrogen receptor (ER)-dependent and ER-independent pathways.^{27–29} This is consistent with the finding that phytoestrogens, which have steroidal structures similar to estrogens and are found in a variety of plant foods, inhibit PCa cell proliferation.⁴⁹ Indeed, ER β has been detected in human PCa cell lines, including LNCaP, PC-3 and DU145, and in normal and malignant prostate tissues, whereas ER α is expressed in PC-3 cells and in stromal (not epithelial) cells of the prostate.^{30–32} Furthermore, it is suggested that loss of ER β in PCa tissues is associated with tumor progression.^{32,33} These findings might be able to

explain the evidence that administration of DES could be more effective than other androgen ablation therapies in suppressing PCa growth if unfavorable side effects of DES are not considered.^{12,13} On the other hand, we previously showed that a natural estrogen, 17 β -estradiol, but not DES, increased AR transcriptional activity in PCa cells.³⁴

LH-RH Agonists and Antagonists

The introduction of LH-RH analogues, obtaining medical castration, has led to a dramatic change in the treatment of advanced PCa.³⁵ In the United States, two LH-RH agonists are commercially available: leuprolide acetate and goserelin acetate.

LH-RH is generally secreted by the hypothalamus in pulses, leading to pulsatile secretion of LH by the pituitary. This in turn promotes testosterone secretion by the Leydig cells of the testes. However, constantly high levels of LH-RH that occur with agonist administration down-regulate the receptors in the pituitary, inhibit LH secretion, and thereby reduce testosterone production. In addition, some studies have suggested a direct inhibitory effect of LH-RH via LH-RH receptors in PCa cells.^{36,37}

Several randomized studies showed the equivalent effectiveness between surgical castration and LH-RH agonist administration.^{38,39} Recently, depot LH-RH agonist preparations have been developed, which last 3 to 4 months and have the same efficacy as classical preparations.⁴⁰ Thus, the depot preparations have now become the most widely used form of androgen deprivation. Side effects of LH-RH agonists include hot flashes, reduced libido, and osteoporosis.⁴¹ In addition, LH-RH agonists often cause an initial surge of LH release, with a corresponding increase in serum testosterone and DHT lasting 1 to 2 weeks. This surge may stimulate PCa growth with a worsening of related symptoms, which is known as the flare phenomenon.⁴² Therefore, administration of an antiandrogen or estrogen for a week before and during the first few weeks of LH-RH agonist therapy is often used in an attempt to limit the clinical sequelae caused by this hormonal surge.^{42,43}

LH-RH receptor antagonists recently have been developed for androgen deprivation.⁴⁴ Since abarelix, the first peptide antagonist, directly blocks the binding of LH-RH to its receptor without agonist activity, there is no initial flare phenomenon as occurs with LH-RH agonists.^{44,45} Recent

clinical studies have demonstrated that abarelix monotherapy achieves medical castration and a reduction of serum PSA levels to the same extent achieved by LH-RH agonists.^{46–48} However, long-term follow-up studies are necessary to determine whether LH-RH antagonists can be routinely used for advanced prostate cancer.

Combined Androgen Blockade (CAB)

Monotherapy with surgical or medical castration results in marginal or no decline of adrenal androgens that not only can be converted to testosterone/DHT but are likely to possess intrinsic androgenic activity.^{9,10,49} Thus, men who undergo castration still have relatively high levels (up to 40%) of DHT and 5%–10% of testosterone.^{7,50} The basis of CAB (also called maximal androgen blockade) is concomitant neutralization of both testicular and adrenal sources of androgens. CAB consists of treatment with a LH-RH agonist or surgical castration combined with a non-steroidal antiandrogen. Antiandrogens include a number of compounds that interfere with the binding of androgens to the AR in the target cell, which ultimately prevents the activation of AR pathways in those cells. CAB has been advocated as the most effective hormonal treatment for patients with advanced PCa. However, this approach implies increased side effects and cost, and there are few supportive data showing a meaningful improvement in survival associated with the addition of antiandrogen.^{51,52}

Several early, randomized trials demonstrated a significant survival advantage of CAB in patients with advanced PCa, compared to castration alone.^{53–56} In 1998, however, Eisenberger *et al.*⁵⁷ reported a trial of 1387 patients with metastatic PCa who were randomized to surgical castration and placebo vs. flutamide. There were no differences in progression-free or overall survival between the two arms. Several factors were hypothesized to explain the discrepancy between the results of this study and earlier reports. First, patients in this study might have had less aggressive disease. Second, castration with a LH-RH agonist, especially a daily regimen of leuprolide injections in the first study,⁵³ might not have been as complete as surgical castration. Third, the LH-RH agonist plus placebo group may have experienced initial flare leading to worsening the disease. In 2000, the Prostate Cancer Trialists' Collaborative Group⁵² published a meta-analysis

of 27 trials of CAB vs. monotherapy involving 8275 patients with advanced PCa. The difference in the 5-year survival rate was not statistically significant (25.4% with CAB vs. 23.6% with castration alone). However, a statistically significant difference ($p < 0.02$) in favor of castration plus a non-steroidal antiandrogen was observed. More recently, another meta-analysis of 20 randomized trials concluded that there was a 5% improvement in 5-year survival (30% vs. 25%) with CAB.⁵⁸ However, only 7 of the 20 studies might be considered as high-quality trials and no significant improvement with CAB was seen in the meta-analysis of these 7 studies. In summary, recent data show that CAB provides a minimal advantage (up to 5% improvement in 5-year survival) over castration monotherapy. It is generally recommended to use an antiandrogen before and during the first several weeks of LH-RH agonist therapy to prevent possible symptoms of the flare. With these data, prolonged treatment beyond 1 month with CAB may not be the first choice of hormonal therapy for advanced PCa.

Antiandrogen Monotherapy

There are two types of antiandrogens, steroidal, such as cyproterone acetate (CPA) and megestrol acetate, and non-steroidal, such as flutamide, nilutamide, and bicalutamide. As noted, antiandrogens are generally used in conjunction with castration as CAB. However, castration based approaches are usually associated with side effects, which have a negative impact on quality of life (QOL). Monotherapy with a (non-steroidal) antiandrogen is becoming an increasingly attractive alternative therapeutic approach. Most of non-steroidal antiandrogens increase within normal physiological range the serum levels of androgens due to the suppression of the pituitary feed-back. Thus, this means of androgen blockade can preserve gonadal function and therefore provide potential QOL benefits, particularly in terms of retained potency and libido, no muscle weakness, and less bone demineralization.

Flutamide

Flutamide was the first non-steroidal antiandrogen that was widely used as a component of CAB. However, the use of flutamide monotherapy for advanced PCa has not been extensively studied in phase III trials.⁵⁹ Initial open studies assessing the clinical efficacy of flutamide as monotherapy

were reviewed by Delaere and Van Thillo.⁶⁰ Among approximately 500 previously untreated patients with advanced PCa, 68% achieved at least a partial response. But most studies were relatively small, and there seemed to be differences in the criteria of response. Several trials have compared the efficacy of flutamide as monotherapy with that of DES, orchiectomy, or CAB. Boccardo reviewed these studies and found no significant differences in response rates/duration among these groups.⁵² In a double-blind randomized study to compare the efficacy of flutamide with 3 mg/day DES,²¹ however, DES produced significantly longer overall survival than flutamide (43.2 months vs. 28.5 months). Because some adverse effects, such as hepatotoxicity, were noted, the rate of treatment withdrawal for any drug-related adverse events was highest with flutamide among 3 non-steroidal antiandrogens.⁵⁹ There have been no comparative studies of the efficacy of different non-steroidal antiandrogens as monotherapy.

Nilutamide

No randomized studies of monotherapy with nilutamide or comparative studies with any other hormonal therapy have been reported. One small study (26 patients) evaluated the efficacy of nilutamide as monotherapy, demonstrating that 21 (91%) of the 23 evaluable previously untreated patients with metastatic PCa had a response, with a median overall survival of 23 months.⁶¹ The survival rate in this study might be less than that achieved by CAB with nilutamide.⁶² In addition, nilutamide was associated with a high incidence (31%) of visual problems (light-dark adaptation disorders).⁶¹ Other unique adverse effects of nilutamide, when used as either monotherapy or a component of CAB, include alcohol intolerance and interstitial pneumonitis.^{61,62} Nilutamide has been reported to cause a higher incidence of nausea and vomiting than the other non-steroidal antiandrogens, whereas the incidence of diarrhea and gynecostasia is lower with nilutamide than flutamide.^{59,62} These results may discourage conducting larger trials with nilutamide monotherapy.

Bicalutamide

Of available non-steroidal antiandrogens, bicalutamide as monotherapy has been most extensively studied. In early comparative trials using

bicalutamide at 50 mg/day, castration was shown to be superior to bicalutamide monotherapy, in terms of survival rate in patients with metastatic disease.⁶³ However, subsequent trials with bicalutamide at 100 or 150 mg/day have revealed equivalent efficacy between bicalutamide monotherapy and surgical or medical castration.^{52,64,65} Other comparative studies also showed no statistically significant differences in survival between bicalutamide at 150 mg/day monotherapy and CAB (castration with flutamide or nilutamide) with better tolerability in the bicalutamide monotherapy group.^{66,67} Bicalutamide at 150 mg/day has been shown to have a more favorable side effect profile than flutamide and nilutamide,⁵⁹ although there was still a high risk of gynecomastia and breast pain. Since bicalutamide has a longer elimination half-life of approximately 6 days than flutamide (6 hours) or nilutamide (56 hours), it can be given once daily vs. flutamide (or nilutamide in many studies) dosed 3 times daily.^{62,68,69} The most recent and largest trials involving 8113 patients confirmed these observations (clinical efficacy, QOL benefit, and tolerability).⁷⁰ Thus, bicalutamide at 150 mg/day is thought to be an appropriate dosage, and this treatment, either alone, referred to as peripheral androgen blockade, or as adjuvant therapy, could be a standard option in patients with localized or locally advanced PCa.

CPA

CPA, a progestational antiandrogen, was the first antiandrogen used for the treatment of advanced PCa in Europe. It acts as an AR antagonist, as well as causes partial suppression of pituitary gonadotropins, which results in a rapid and sustained 70% decrease in testosterone levels.⁷¹ Therefore, CPA, as a single agent, may yield CAB. In clinical studies, there were no significant differences in tumor response rates or disease specific survival between CPA and any other forms of androgen deprivation, such as surgical castration, estrogens, LH-RH agonists, and non-steroidal antiandrogens.^{59,72} Unfortunately, CPA has been reported to induce severe cardiovascular complications in about 10% of patients, although the rate is lower than those of DES (up to 33%).¹⁸ Other complications include gynecomastia, loss of libido, erectile dysfunction, and central nervous system effects such as headache, fatigue, and weakness

that are possibly attributable to the lowering of serum testosterone levels. Therefore, the use of CPA as monotherapy might be limited to those who find surgical castration unacceptable. In addition, CPA can be used to block LH-RH induced flare reactions and to suppress surgical or medical castration-related hot flashes.^{71,72}

Neoadjuvant/Adjuvant Hormonal Therapy with Radical Prostatectomy

Neoadjuvant Hormonal Therapy

Radical prostatectomy is a treatment modality which can offer the possibility of PCa cure if surgical margins are negative. However, surgical attempts for a cure in patients with apparently localized PCa often fail because the cancer is incompletely resected possibly due to clinical understaging before the surgery or micrometastases existing at the time of surgery. The theoretical purposes of neoadjuvant treatment are to lower the pathological stage, reduce the likelihood of positive margins, eliminate micrometastases, and ultimately increase patient survival.

Laboratory experiments using the Shionogi tumor model support this rationale.⁷³ Pathologically positive surgical margins were detected in 66% of mice undergoing wide tumor excision (group 1) and in 33% of mice treated with neoadjuvant castration 10 days before wide excision of progressed tumor (group 2). Subsequent androgen-independent tumor recurrences were seen in 92% of group 1 and in 44% of group 2. There were statistically significant differences in overall tumor-free survival rates (group 1: 20% vs. group 2: 56%, $p < 0.05$).

Several prospective randomized trials have been performed to investigate the significance of neoadjuvant androgen deprivation for 3 months before radical prostatectomy.⁷⁴⁻⁷⁷ Most studies demonstrated a significant reduction in prostate volume and margin-positive rates in the patient groups with neoadjuvant androgen deprivation. Unfortunately, these studies failed to show a significant improvement in seminal vesicle invasion, lymph node involvement, or PSA recurrence. None showed an advantage of neoadjuvant treatment in overall survival. Possible reasons for this discrepancy include an insufficient duration of neoadjuvant hormonal therapy. Gleave *et al.*⁷⁸ observed 547 patients who were randomized to

receive neoadjuvant CAB for 3 or 8 months prior to radical prostatectomy. Positive margin rates were significantly lower in the 8-month than 3-month group (12% vs. 23%, $p = 0.0106$), and the authors concluded that the optimal duration of neoadjuvant androgen deprivation is longer than 3 months. However, rates of local or biochemical recurrence and long-term survival were not reported in this study. In addition, an 8-month delay of surgery might carry a high risk for patients with androgen-independent tumor. Neoadjuvant hormonal therapy should therefore remain under investigation.

Adjuvant Hormonal Therapy

There are a few retrospective studies showing a significantly positive effect of adjuvant hormonal therapy following radical prostatectomy on disease-free survival.^{79,80} In a large retrospective, non-randomized series from the Mayo Clinic, continuous hormonal therapy prolonged overall survival in patients with nodal metastases who underwent radical prostatectomy. However, in earlier analyses, the benefits of this treatment were seen only in men with DNA diploid cancers.⁸⁰ Zincke *et al.* also retrospectively reviewed 707 patients with stage pT3b disease, including 157 patients who received adjuvant hormonal therapy, and found that adjuvant hormonal therapy significantly improved the mean 10-year survival rates.⁸¹ The Eastern Cooperative Oncology Group (ECOG),⁸² in a prospective randomized clinical trial, investigated the effect of adjuvant hormonal therapy in 98 patients with clinically localized PCa and lymph node metastases. Androgen deprivation (goserelin or surgical castration) was initiated within 12 weeks of radical prostatectomy and pelvic lymphadenectomy in the adjuvant group, whereas, in the observation group, androgen deprivation was delayed until disease progression (almost always initiated at diagnosis of metastases). After 7.1 years of median follow-up, immediate treatment was associated with significant advantages in overall (85% vs. 64%; $p = 0.02$) and cause-specific (93% vs. 68%; $p = 0,001$) survival rates. The ECOG study has been criticized because of its relatively small number of patients and lack of central pathological review to determine Gleason grades.⁸³ However, a recent reanalysis of Gleason grades by central pathology review reveals no

significant changes in outcomes, including survival.⁸⁴ With mean follow-up of 10 years highly significant differences in overall (72% vs. 49%; $p = 0.025$) and cause-specific (87% vs. 57%; $p = 0.001$) survival rates were observed.⁸⁴ Adjuvant therapy with antiandrogen, such as flutamide⁸⁵ or bicalutamide,⁷⁰ has also been reported to reduce biochemical recurrence in a broad spectrum of post-prostatectomy patients. However, these studies are too premature to evaluate survival or other meaningful outcomes.

Hormonal Therapy with Radiation Therapy/ Brachytherapy/ Chemotherapy

Radiation Therapy

Zietman *et al.*⁸⁶ demonstrated that prior androgen deprivation enhanced the effect of radiation on eradicating androgen-sensitive Shionogi mouse mammary tumors. An additive effect of androgen deprivation and radiation on apoptosis was also observed in both Dunning rat prostate tumors and LNCaP human PCa cells.^{87,88} Also a recent study using a xenograft model demonstrated a synergistic inhibitory effect of castration and radiotherapy.⁸⁹ LNCaP-bearing mice treated with castration prior to radiation had significantly decreased mean tumor volume and serum PSA levels, compared to those treated with castration or radiation alone, throughout the observation period up to 11 weeks after initiation of treatment. Interestingly, in an androgen-sensitive Dunning rat prostate tumor model, testosterone treatment after castration and radiotherapy failed to stimulate tumor growth, suggesting cancer cells lost their androgen sensitivity through irradiation.^{90,91} Moreover, in this model, castration 14 days prior to radiation was found to be superior in suppressing tumor growth, compared to androgen deprivation alone, radiation alone, or androgen deprivation 3 days after radiation.⁹¹

Three prospective studies revealed statistically significant improvements in overall survival in favor of early hormonal therapy in the radiotherapy setting. The European Organization for Research and Treatment of Cancer Genitourinary Group conducted a randomized phase III trial comparing external irradiation alone with combined therapy, with concomitant plus adjuvant androgen deprivation plus radiation, in locally

advanced PCa patients.⁹² From 1987 to 1995, 415 patients with WHO grade 3, stage T1-2 cancers, or stage T3-4 tumors of any grade were randomized to (1) radiotherapy plus goserelin, starting on the first day of irradiation and continuing monthly for 3 years (CPA was also given during the first month to prevent flare phenomena), *vs.* (2) radiotherapy alone followed by the same hormonal therapy upon clinical progression. With median follow-up of 66 months, 5-year clinical disease-free survival was 74% in the early hormonal therapy group and 40% in the control group ($p = 0.0001$), and 5-year overall survival was 78% and 62%, respectively ($p = 0.0002$).⁹² Five-year local disease control was particularly impressive (although biopsies were not done), with 98% in the combined treatment group *vs.* 74% in the control arm being clinically free of local recurrence.

The Radiation Therapy Oncology Group (RTOG) has conducted several large, prospective randomized trials to assess the potential benefit of early *vs.* late and of short-term *vs.* long-term hormonal therapy in PCa patients treated with radiotherapy. In the RTOG protocol 85-31, 977 patients with T1-2 N1 or T3 non-metastatic disease, including post-prostatectomy cases, were randomized to receive goserelin starting at the last week of radiotherapy, and continuing indefinitely, or radiotherapy with deferred androgen deprivation at relapse. While initial publication of results at a median follow-up of 4.5 years reported that immediate goserelin treatment significantly improved local and distant disease control as well as disease-free survival (all $p < 0.0001$), there was no difference in overall survival.⁹³ However, a recent update of data at a 7.3-year mean follow-up demonstrated significant improvement in overall survival with estimated 10-year survivals being 53% and 38% in the immediate and deferred treatment groups, respectively.⁹⁴

A parallel trial (RTOG 86-10) was performed to evaluate the efficacy of short-term hormonal therapy in PCa patients receiving definitive radiation therapy.⁹⁵ A total of 456 patients with T2-4 tumors were randomized to receive CAB with goserelin and flutamide for 4 months (2 months before and 2 months during radiotherapy) with radiotherapy *vs.* radiotherapy alone, with salvage hormonal therapy with orchiectomy, LH-RH agonist, or antiandrogen to be initiated when clinically indicated for relapse or progression of disease. At median follow-up of 6.7 years, early hormonal therapy was associated with a significant improvement in local and

distant disease control and disease-free survival. Fewer patients in the combination arm (45%) received salvage hormonal therapy than those in the control arm (63%) ($p < 0.001$). However, no significant differences between the two arms were apparent for either overall survival at 5 years (71% vs. 69%) or at 8 years (53% vs. 43%).

Horwitz *et al.*⁹⁶ compared the above two studies and concluded that statistically significant improvements in biochemical disease-free status, distant metastases failure, and cause-specific failure rates were observed for adjuvant long-term hormonal therapy compared with short-term adjuvant hormonal therapy or radiotherapy alone in patients with locally advanced non-metastatic PCa.

Hanks *et al.*⁹⁷ reported the results of another randomized RTOG study (protocol 92-02) comparing short-term and long-term hormonal therapy involving 1554 men with T2c-4 disease and a PSA < 150 ng/ml who received goserelin and flutamide 2 months before and 2 months during radiotherapy plus either no further therapy or 24 months of additional goserelin alone. With median follow-up of 4.8 years, long-term androgen deprivation led to significantly improved local ($p = 0.0001$) and distant ($p = 0.001$) disease control and a trend in longer disease-free survival (92% vs. 87%, $p = 0.07$). However, there was no significant difference in 5-year overall survival between the two arms (78% vs. 79%). A subset analysis comparing the results from centrally reviewed Gleason scores 8–10 patients from the RTOG 85-31 also showed a statistically significant advantage in patients receiving long-term androgen deprivation in estimated 5-year overall survival (80% vs. 69%; $p = 0.02$) and disease-free survival (90% vs. 78%; $p = 0.007$) rates.

Brachytherapy

Brachytherapy is increasingly used in patients with localized, low- to intermediate-grade PCa. Neoadjuvant androgen deprivation therapy is commonly given to patients who have a large prostate, to downsize the prostate, making the brachytherapy procedure easier and more feasible. Indeed, it has been reported that prostate volume was reduced by up to 40% after 3 months of androgen deprivation therapy.⁷⁸ Thus, combining hormonal therapy with prostate brachytherapy may reduce brachytherapy-related

morbidity and improve patient outcome. However, no additional benefits of adjuvant hormonal therapy over the prostate brachytherapy on survival were apparent.⁹⁸ Because no prospective, randomized studies have been published, the impact of hormonal therapy in conjunction with brachytherapy remains unclear.

Chemotherapy

Previous studies have established the role of chemotherapy in the palliation of symptoms in patients with PCa after failure of hormonal therapy,^{99,100} although its clear survival benefit is not reported. Among a variety of drugs, mitoxantrone- and estramustine-based regimens have been extensively studied and shown to have a significant palliative benefit.¹⁰⁰ Estramustine has an estradiol moiety and has been used in PCa patients for several decades. Estramustine, as a single agent, decreases serum testosterone to castration levels, with significant cardiovascular toxicity. Combination regimens of chemotherapy with other hormonal therapies have also been investigated for locally advanced, presumably androgen-sensitive, PCa. In a study by Pettaway *et al.*,¹⁰¹ 33 high-risk patients (either clinical stage T3 or Gleason score >7) were treated with ketoconazole, doxorubicin, vinblastine and estramustine plus a LH-RH agonist and an antiandrogen for 12 weeks before radical prostatectomy. Thirty-three percent of them were found to have prostate-confined disease at the time of surgery. In another multicenter study, 50 locally advanced patients were treated with paclitaxel, estramustine, and carboplatin plus a LH-RH agonist for 4–6 months. Of the 23 patients who underwent radical prostatectomy, 45% of them attained organ-confined disease.¹⁰⁰ There were no comparisons of combination regimen to hormonal therapy alone.

Several *in vitro* studies investigated combinations of chemotherapy and hormonal therapy. Kreis *et al.*¹⁰² showed synergistic effects on growth inhibition of either androgen-sensitive LNCaP, androgen-insensitive DU145 and PC-3, or all cell lines, using combinations of estramustine plus flutamide or PSC833 (Sandoz) plus bicalutamide. Other studies demonstrated that androgen deprivation could trigger apoptosis of androgen-sensitive cancer cells via a transient increase in cytosolic calcium, resulting in activation of Ca²⁺- and Mg²⁺-dependent endonucleases.^{103,104}

Therefore, chemotherapy may become more effective when combined with androgen deprivation. In contrast, androgen deprivation was also shown to promote androgen-dependent cells to enter the G₀ phase of the cell cycle instead of undergoing apoptosis.¹⁰⁵ Therefore, these cells might be more difficult to eradicate with subsequent chemotherapy.

Intermittent Androgen Deprivation

Intermittent androgen blockade (IAB) aims at delaying the onset of androgen-independent growth of PCa, as well as reducing side effects and costs. Laboratory studies have supported the hypothesis that IAB prolongs the initial androgen-sensitive period. Langelier *et al.*¹⁰⁶ showed that intermittent androgen suppression could delay the emergence of androgen-independent clones induced in LNCaP after long-term culture with androgen deprivation. Akakura *et al.*¹⁰⁷ and Sato *et al.*¹⁰⁸ studied IAB in castrated animals bearing androgen-dependent tumors treated with intermittent exposure to androgens. The results suggest that IAB induces multiple apoptotic regressions of androgen-dependent PCa and prolongs the time to androgen-independent progression, compared to continuous androgen deprivation.

The first attempt at IAB was reported in 1986.¹⁰⁹ Twenty patients with advanced PCa were treated with intermittent hormonal therapy (DES in 19 cases and flutamide in one case) until subjective improvement was noted, with a mean initial treatment duration of 10 months (range 2–70 months). The therapy was then stopped, and re-started when tumors relapsed, with a mean interval time of 8 months (range 1–24 months). All relapsed patients responded to re-administration of the drug. Patients had better QOL during the break in the treatment and DES-induced erectile dysfunction was reversed in 9 of 10 patients within 3 months of treatment interruption.

The availability of agents that induce reversible medical castration, such as LH-RH agonists, and serial serum PSA measurements after the mid-1980s, made it easier to introduce IAB and to monitor disease activity. Several clinical studies of IAB have been reported.^{110–113} These intermittent hormonal therapies consist of an initial androgen deprivation period using a LH-RH agonist with or without a non-steroidal antiandrogen of usually between 6 and 9 months, followed by an off-therapy interval

(6–15 months). When PSA values meet threshold criteria (>5 – 10 ng/ml), treatment is resumed. Most of the initial responders (57%–100%) respond to re-treatment. This cyclic treatment continues until the patient develops androgen-independent tumors. While off-treatment, many patients had improvement in libido, erection, and energy, as well as fewer hot flashes. However, retrospective comparison of survival in these patients was similar to those who were treated with continuous androgen blockade. Interestingly, in certain patients, especially in those who received androgen deprivation for longer periods, gonadal function and serum testosterone levels did not recover.¹¹⁴ These findings suggest that intermittent administration of LH-RH agonists may achieve continuous androgen deprivation, resulting in reduction of cost. A recent study also showed that the median duration of castration levels of serum testosterone was 5.5 months (range 3.5–10 months) after a single injection of long-acting (3-month) depot LH-RH agonist and that the method of re-dosing LH-RH agonists based on serum testosterone levels appeared efficacious, safe, and cost-effective.¹¹⁵

The debate continues as to whether IAB improves survival. Large, randomized, phase III clinical trials, comparing intermittent vs. continuous androgen deprivation are currently ongoing to assess endpoints including survival, time to androgen-independent progression, and QOL. Furthermore, intermittent triple androgen blockade (TrAB), another form of IAB using a 5α -reductase inhibitor, finasteride, during off-treatment periods, is also being evaluated.¹¹⁶

5 α -Reductase Inhibitors

Two 5α -reductase enzymes have been identified: type 1, the predominant enzyme in extraprostatic tissues, such as skin and liver; and type 2, predominantly expressed in the prostate.⁶ The type 2 5α -reductase has been implicated in, at least partially, the regulation of early prostate growth as well as later hyperplastic growth. Therefore, finasteride, the first 5α -reductase inhibitor specific for the type 2 enzyme, which significantly decreases levels of both serum and intraprostatic DHT by 70%–80%, reduces the total size of the prostate gland.¹¹⁷ Thus, finasteride treatment has been a useful form of androgen deprivation for benign prostatic hyperplasia (BPH), with

fewer adverse effects than antiandrogen treatment. However, the therapeutic activity of finasteride itself on PCa has not been identified. The effect of finasteride in conjunction with other forms of hormonal therapy has been investigated. In addition to TrAB,¹¹⁶ sequential androgen blockade (SAB), a combination therapy with finasteride plus an antiandrogen or an LH-RH agonist, has been evaluated and has been shown to substantially decrease the PSA levels in men with metastatic PCa while maintaining sexual potency in most patients.^{118,119} However, phase III studies, comparing SAB with traditional hormonal therapy, such as CAB, have not been conducted and the survival benefit thus remains unknown.

The benzoquinoline, LY320236, is a newer and dual (type 1/2) 5α -reductase inhibitor currently in phase I trials of PCa.¹²⁰ The antitumor activity of benzoquinoline has been demonstrated in human PCa xenograft models.

Concluding Remarks

Many options involving the AR, androgens, and their antagonists are available for the treatment of PCa (Fig. 1). Numerous clinical studies have shown equivalent effects on therapeutic benefits by different hormonal treatment strategies. Each treatment strategy/hormonal agent has favorable and unfavorable effects (Table 1). Patients with advanced PCa will clearly benefit from androgen deprivation-based treatments for symptom palliation and improvement of their QOL. However, whether these therapies prolong survival when administered before there are symptoms caused by disease progression remains controversial. Thus, despite a number of previous clinical and experimental studies, finding suitable patients, timing of, and options for hormonal therapy remain problematic.¹²¹ Data from recent studies support the premise that an earlier treatment in patients' disease course likely leads to better outcomes,^{82,84,92} but it is not easy to predict the best timing of hormonal therapy for patients with asymptomatic advanced disease. Observation may still be a reasonable choice for these patients.

Currently, available options for hormonal therapy almost never lead to cures in patients with advanced PCa because these patients eventually develop androgen-independent tumors. In addition, another type of failure

of hormonal therapy, antiandrogen withdrawal syndrome, has been observed in a significant number (15%–80%) of patients treated with CAB. Although the exact mechanisms for androgen-independent PCa and antiandrogen withdrawal syndrome are far from being fully understood, possible mechanisms were discussed in recent review papers.^{122,123} To improve overall survival of patients with advanced PCa, novel treatment strategies that prolong the androgen-dependent state, but will not induce antiandrogen withdrawal syndrome, and that are effective against androgen-independent disease, need to be identified. Furthermore, it may be necessary to explore more individualized approaches, such as selectively blocking the activated AR pathway in cancer cells. Finally, second-line hormonal therapy and PCa chemoprevention using hormonal therapy are other interesting topics that are not discussed in this chapter (please refer to Chapter 6 in this volume).

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