Initial therapy for castration sensitive metastatic prostate cancer

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INTRODUCTION — The critical role of androgens in stimulating prostate cancer growth was established in 1941 by Charles Huggins [1,2]. These findings led to the development of androgen deprivation therapy (ADT) as the treatment for patients with advanced prostate cancer.

Although androgen deprivation therapy (ADT) is palliative, it can normalize serum levels of prostate specific antigen (PSA) in over 90 percent of patients and can produce objective tumor responses in 80 to 90 percent. This antitumor activity can improve quality of life (QOL) by reducing bone pain as well as the rates of complications (eg, pathologic fracture, spinal cord compression, ureteral obstruction).

The duration of response to ADT for patients with metastatic disease is highly variable, and most prostate cancer patients eventually experience disease progression despite treatment. Patients who have progressed while on ADT are said to have castration resistant disease, although such tumors may remain responsive to additional therapies directed against androgenic stimulation of the prostate cancer.

Docetaxel was subsequently shown to prolong survival in men with castration resistant prostate cancer. Contemporary research has demonstrated that chemohormonal therapy combining docetaxel with ADT offers a clinically meaningful survival advantage for patients with castration sensitive disease and a high tumor burden. (See "Chemotherapy in castrate-resistant prostate cancer", section on 'Chemotherapy-naive patients: Docetaxel' and 'Chemohormonal therapy' below.)

The initial therapy for men with castration sensitive metastatic prostate cancer will be reviewed here. An overview of the treatment of disseminated prostate cancer is presented separately, as are special considerations for patients whose only manifestation of disseminated disease is a rising serum PSA. (See "Overview of the treatment of disseminated prostate cancer" and "Rising serum PSA after treatment for localized prostate cancer: Systemic therapy".)

ANDROGEN DEPRIVATION THERAPY — Androgen deprivation therapy (ADT) with lowering of serum testosterone levels to castrate levels remains the primary approach to the systemic treatment of castration sensitive metastatic prostate cancer and a low tumor burden. In addition, ADT is an integral component of therapy along with docetaxel chemotherapy for men with a high tumor burden. (See 'Chemohormonal therapy' below.)

ADT can be accomplished either by surgical orchiectomy (castration) or medical orchiectomy (using either a gonadotropin releasing hormone [GnRH] agonist or a GnRH antagonist). In some cases, antiandrogens have been combined with a GnRH agonist to block the effects of androgen produced by the adrenal gland and produce a combined androgen blockade. Both medical orchiectomy and surgical orchiectomy are appropriate methods for lowering serum testosterone levels in men with advanced castration sensitive prostate cancer [3-5]. The decision between medical and surgical treatment is based upon a variety of factors including patient preference, cost, and treatment availability. (See 'Surgical orchiectomy' below and 'Medical orchiectomy' below and 'Combined androgen blockade with antiandrogens' below.)

Historically, estrogens were also used to suppress serum testosterone levels. Estrogens inhibit the release of GnRH from the hypothalamus, thus suppressing pituitary luteinizing hormone release and thereby reducing testicular production of testosterone. Diethylstilbestrol (DES) was extensively studied as an alternative to surgical orchiectomy for the initial management of metastatic prostate cancer prior to the development of GnRH agonists. However, two large randomized trials conducted by the Veterans Administration Cooperative Urological Research Group (VACURG) found that DES at a dose of 5 mg/day significantly increased the risk of dying from heart disease or stroke, and that DES did not provide any advantage compared with surgical orchiectomy in terms of overall survival [6,7].

Guidelines from the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN) and the European Association of Urology (EAU) recommend ADT using either medical orchiectomy or surgical orchiectomy as the initial hormonal therapy for men with advanced prostate cancer [3-5]. The decision between medical and surgical treatment is based upon a variety of factors including patient preference, cost, and treatment availability.

Surgical orchiectomy — Bilateral orchiectomy is a relatively simple, cost-effective procedure [8]. Following surgery, serum testosterone levels rapidly decrease to castrate levels [9], and this is usually associated with improvements in bone pain and other disease-related symptoms [2].

Although orchiectomy is used much less frequently than medical castration in North America and Europe, it remains a useful alternative when an immediate decrease in testosterone is necessary (eg, impending spinal cord compression) or when costs or adherence to medical therapy are an issue. In many countries, bilateral orchiectomy remains the standard of care for initial hormone therapy of metastatic prostate cancer.

The psychological impact of surgical castration is also an important factor for men choosing between surgery and medical treatment. In a study of 159 men with metastatic prostate cancer who were provided with standard information regarding the costs, benefits, and risks of orchiectomy, only 22 percent chose orchiectomy [10]. However, the benefits of lower overall cost, avoidance of injections for continued medical castration, and potentially fewer clinic visits may make orchiectomy more appealing in the current era of escalating health care costs.

The psychological effects of orchiectomy may be ameliorated with placement of testicular prostheses or with modification of the total orchiectomy to a subcapsular orchiectomy, in which the tunica albuginea and epididymis remain intact, providing a cosmetic effect in the scrotum [11,12].

Medical orchiectomy

Gonadotropin releasing hormone agonists — Medical castration using a gonadotropin releasing hormone (GnRH) agonist was first reported in 1982 [13].

Mechanism of action — Synthetic GnRH analogs have greater receptor affinity, reduced susceptibility to enzymatic degradation, and are approximately 100-fold more potent than the natural GnRH molecule [14]. GnRH agonists bind to the GnRH receptors on pituitary gonadotropin-producing cells, causing an initial release of both luteinizing hormone (LH) and follicle stimulating hormone (FSH), which causes a subsequent increase in testosterone production from testicular Leydig cells (figure 1).

This transient rise in LH when GnRH therapy is initiated can cause a surge in serum testosterone, which may stimulate prostate cancer growth. This "flare" may cause an increase in bone pain, bladder obstruction, or other symptoms due to prostate cancer [15]. Thus, initial treatment with GnRH alone is contraindicated in men with severe urinary tract obstruction or painful bone metastases. The flare phenomenon can be effectively prevented with antiandrogen therapy, which blocks the effect of the increased serum testosterone [8]. (See 'Combined androgen blockade with antiandrogens' below.)

After about one week of therapy, GnRH receptors are down-regulated on the gonadotropin-producing cells, with a decline in the pituitary production of LH and FSH [16]. The fall in serum LH leads to a decrease in serum testosterone to castrate levels within three to four weeks after the start of treatment [17]. Continued treatment maintains serum testosterone at castrate levels.

The decrease in testosterone production is generally reversible upon cessation of GnRH agonist therapy. However, testosterone production does not always return to baseline levels and may be related to the duration of GnRH agonist therapy, patient age, and other factors [18,19].

Formulations — GnRH agonists approved for parenteral administration include leuprolide, goserelin, triptorelin, buserelin, and histrelin. Buserelin is available in both a parenteral and nasal formulation.

Depot formulations are widely used. These initially were available to suppress testosterone levels for about one month; even longer acting formulations are now available and commonly used. The longest lasting is a leuprolide formulation delivered by a small osmotic pump encased in a titanium cylinder. This is implanted subcutaneously in the upper arm where it can deliver the drug for up to one year. Castrate levels of testosterone are achieved and sustained for the entire year of implantation [20,21]. Annual removal and replacement is a short, outpatient procedure.

Serum testosterone level — The objective of ADT is to lower the serum testosterone level at least to the same extent as that achieved with surgical orchiectomy [22]. Historically, this has correlated with a level of <50 ng/dL, although contemporary laboratory testing indicates that testosterone levels decline to <20 ng/dL after orchiectomy [9]. However, there are no clinical trials that clearly correlate serum testosterone level with clinical response and outcome.

Our practice is consistent with the current guidelines from the National Comprehensive Cancer Network (NCCN), which use a serum testosterone level of <50 ng/dL. Additional hormonal maneuvers can be considered if adequate suppression of serum testosterone cannot be achieved with initial treatment [23]. Rechecking the serum testosterone level is especially important if the anticipated clinical or biochemical response to treatment has not been achieved.

GnRH agonists versus orchiectomy — Unlike orchiectomy, medical castration with GnRH agonists offers the potential for reversing hypogonadal symptoms upon cessation of therapy. In addition, GnRH agonists avoid the psychological issues associated with surgical castration.

A meta-analysis of 10 trials involving 1908 patients comparing a GnRH agonist with orchiectomy found equivalence in overall survival, progression-related outcomes, and time to treatment failure [24]. At two years, survival with a GnRH agonist was not statistically worse (hazard ratio for death 1.13, 95% CI 0.92-1.39, compared with orchiectomy). In this meta-analysis, there were no significant differences in efficacy between leuprolide, goserelin, and buserelin.

GnRH agonists are frequently used with antiandrogens to produce combined androgen blockade either during the initial period of treatment to prevent a disease flare; they also may be used in conjunction with antiandrogens for long-term therapy. (See 'Combined androgen blockade with antiandrogens' below.)

GnRH antagonists — Pure GnRH antagonists (eg, degarelix) were developed to suppress testosterone while avoiding the flare phenomenon observed with GnRH agonists. GnRH antagonists bind to the GnRH receptors on pituitary gonadotropin-producing cells, but do not stimulate an initial release of LH or FSH.

The efficacy of degarelix was established in a phase III trial in which 610 men with prostate cancer were randomly assigned to degarelix (240 mg for one month, followed by monthly maintenance with doses of either 80 mg [n = 207] or 160 mg [n = 201]) or to leuprolide (7.5 mg per month) [25]:

- Degarelix suppressed testosterone levels within three days in 96 percent of patients, an outcome not achieved in patients treated with leuprolide. Suppression of serum testosterone levels was maintained for the duration of the 12-month trial.
- An update from the 2011 Genitourinary Cancers Symposium indicated that the incidence of PSA failure during the study on the degarelix 240/80 schedule was significantly lower than on the leuprolide arm (8.9 versus 14.1 percent, p = 0.05) [26]. However, the incidence of PSA failure during the study on the degarelix 240/160 schedule was 14.2 percent.
- Secondary analyses from the phase III trial reported a greater suppression of serum alkaline phosphatase with degarelix compared with leuprolide. However, the mean baseline serum alkaline phosphatase was lower in the leuprolide arm in all three of the subgroups that were examined, with small numbers of patients per subgroup. Furthermore, whether greater control of serum alkaline phosphatase translates into better control of skeletal metastasis is not known [27,28].
- Local injection site reactions were more frequent with degarelix than with leuprolide (40 versus <1 percent), although no systemic allergic

reactions were reported. A secondary analysis of cardiovascular complications in the phase III trial found a similar cardiovascular safety profile for both agents [29].

- In a follow-up study, patients initially assigned to degarelix were continued on maintenance therapy for up to five years, and those originally assigned to leuprolide were given the opportunity to cross over to degarelix [30]. Treatment with degarelix was well tolerated during this maintenance phase and testosterone suppression was sustained throughout this period.

An individual patient meta-analysis of randomized trials compared degarelix with either leuprolide or goserelin in 1925 men in five trials [31]. Progression-free survival was longer in those treated with degarelix (18 versus 25 percent with progression, p = 0.04). However, treatment in these trials was limited to either 3 or 12 months, and there were only four deaths due to prostate cancer. Additional clinical trials are in progress to determine the long-term clinical outcomes and optimal application of degarelix in men with metastatic prostate cancer.

The need for monthly degarelix injections and long-term experience with GnRH agonists makes the latter the preferred approach in many practices.

Combined androgen blockade with antiandrogens — First generation antiandrogens (eg, flutamide, bicalutamide, nilutamide) bind to androgen receptors and competitively inhibit their interaction with testosterone and dihydrotestosterone. Antiandrogens alone do not block the hypothalamic pituitary axis; testosterone levels are normal or increased. Available antiandrogens and their use as second line endocrine therapies are discussed separately. (See "Secondary endocrine therapies for castration resistant prostate cancer", section on 'Antiandrogens'.)

Antiandrogens are not indicated for monotherapy in previously untreated patients with advanced prostate cancer. However, antiandrogens have a role in conjunction with either medical or surgical castration to produce a combined androgen blockade, which may be useful either to block the side effects associated with the flare phenomenon at the initiation of ADT or for long-term treatment to increase the efficacy of ADT.

Initiation of ADT — We use antiandrogens in the management of men with disseminated prostate cancer during the initiation of treatment with a GnRH agonist, in order to prevent a disease flare due to the transient increase in testosterone levels [8]. (See 'Mechanism of action' above.)

A placebo-controlled trial demonstrated that antiandrogens decrease bone pain at the initiation of GnRH agonists for patients with metastatic prostate cancer [32]. In practice, antiandrogen therapy is often started seven days prior to GnRH agonist initiation for men at high risk of flare symptoms, or concurrently for asymptomatic patients. Antiandrogen therapy is then continued for two to four weeks.

Long-term combined androgen blockade — Long-term administration of antiandrogens has been combined with medical or surgical castration to block the effects of adrenal testosterone in a combined androgen blockade. However, both toxicity and costs are higher and limit the potential benefits of this approach. Our approach is to use monotherapy with a GnRH agonist rather than combined androgen blockade. Both NCCN and ASCO guidelines consider combined androgen blockade an appropriate option but do not make a specific recommendation [3,4].

Numerous randomized trials have compared combined androgen blockade with monotherapy; these are illustrated by two of the largest of these trials:

- Intergroup trial INT 0036 randomly assigned 603 men with metastatic disease to leuprolide plus flutamide or leuprolide alone [33]. Men treated with the combination had significantly longer progression-free and median survival compared with leuprolide alone (16.5 versus 13.9 months and 35.6 versus 28.3 months).
- Intergroup trial INT 0105 randomly assigned 1387 men with metastatic disease to orchiectomy and either flutamide or placebo [34]. Although more patients treated with the combined approach achieved a serum PSA <4 ng/mL (74 versus 62 percent with placebo), the differences in median and progression-free survival were not statistically significant (34 versus 30 months, and 20 versus 19 months, respectively). Withdrawal from the study due to toxicity was significantly more common in those assigned to flutamide (33 versus 10 patients with placebo).

The reasons for the differences in outcome between these two trials are not certain. In INT 0105, ADT utilized orchiectomy [34], while in INT 0036, ADT relied upon daily injections of leuprolide [33]. Lack of adherence to the leuprolide regimen may have led to incomplete androgen deprivation, and therefore a larger benefit when an antiandrogen was added to the treatment in the combined androgen blockade arm [34]. Castrate levels of testosterone were not systematically confirmed in INT 0036.

Several meta-analyses suggest a benefit in five-year survival but not at earlier time points for combined androgen blockade [35-38]. The largest of these, which was conducted by the Prostate Cancer Trialists' Collaborative Group, analyzed individual patient data from 27 randomized trials that included 8275 men (88 percent with metastatic disease) [35]. Combined androgen blockade was associated with a trend toward decreased five-year mortality (70.4 versus 72.4 percent, hazard ratio [HR] 0.96; 95% CI 0.91-1.01). When the seven studies using the steroidal antiandrogen cyproterone acetate were excluded, the reduction in mortality with combined androgen blockade was statistically significant (72.4 versus 75.3 percent; HR 0.92). These data do not resolve the question of whether combined androgen blockade is preferable to medical or surgical orchiectomy alone, since toxicity and costs are higher and potential benefits limited with combined androgen blockade.

There are no data to support the use of more potent androgen receptor antagonists such as enzalutamide alone or in combination with a GnRH agonist, but such approaches are under investigation.

Intermittent androgen deprivation — Intermittent androgen deprivation (IAD) attempts to minimize the adverse effects of medical castration by withdrawing treatment in patients who have responded to ADT and then reinstituting ADT when there is evidence of recurrent or progressive disease.

The biological rationale is twofold. First, prolonged ADT theoretically may facilitate progression from androgen dependence to androgen independence. In addition, many of the acute and chronic side effects of ADT are due to castrate levels of testosterone. Periods of time when men are off therapy may be associated with decreases in these side effects, thereby improving quality of life.

IAD typically involves treatment for either a fixed interval of time or until a maximal response is achieved based upon serum PSA levels. ADT is then withdrawn, and patients are followed for evidence of recurrence. As testosterone production resumes, the side effects of ADT are mitigated, but the risk of disease progression also increases. The patient is followed with PSA measurements, and ADT is reinitiated based on a predefined threshold level of serum PSA (which varies with different practices, but is often between 10 and 20 ng/mL), or with evidence of new metastatic disease.

Metastatic disease — The Intergroup trial INT 0162 (S9346, NCT00002651) compared the impact of IAD with continuous ADT for its impact on overall survival and quality of life in patients with metastatic, hormone sensitive prostate cancer and a serum PSA ≥5 ng/mL [39]. Patients were treated with a combination of a GnRH analog and antiandrogen for seven months. Patients who achieved a PSA ≤4 ng/mL were then randomly assigned to either continuous ADT or IAD. Patients assigned to IAD remained off therapy until they met a prespecified criterion (serum PSA either ≥20 ng/mL or back to original baseline), at which point ADT was resumed. Patients who responded to resumption of ADT could be managed with additional cycles off therapy.

Of the 3040 patients who were enrolled, 1749 patients were randomized and 1535 patients were available for analysis at a median follow-up of 9.8 years:

- INT 0162 was designed as a noninferiority trial based upon overall survival. Survival with IAD was to be considered noninferior if the 95% confidence interval for the hazard ratio excluded 1.20 (ie, a 20 percent difference roughly equal to one year).
- Overall survival measured from the time of randomization was longer with continuous ADT than with IAD (median 5.8 versus 5.1 years, HR 1.10, 95%CI 0.99-1.23). Based upon these results, IAD could not be considered noninferior compared with continuous ADT. In unplanned subset analyses, results were consistent across all subgroups except for those with extensive metastatic disease, where IAD did meet the criteria for noninferiority.
- Quality of life parameters (erectile function, libido, vitality, physical functioning, mental health) were assessed at baseline, and 3, 9, and 15 months after randomization. There were statistically significant improvements in erectile function and mental health at three months with IAD but not at later time points.

IAD was also compared with continuous ADT in a smaller phase III trial from the South European Uroncological Group [40]. Although this trial demonstrated noninferiority in terms of overall survival, only 11 percent of patients had metastatic disease, while the remainder had clinical T3 or T4 disease and were not candidates for definitive therapy.

Based upon the results of the INT 0162 trial, continuous ADT remains the standard of care for patients with metastatic disease.

Rising PSA — The North American JPR.7 trial studied 1386 men with a rising serum PSA but without detectable metastases following definitive radiation therapy [41]. This trial met predetermined criteria for noninferiority for IAD compared with continuous ADT in terms of overall survival. (See "Rising serum PSA after treatment for localized prostate cancer: Systemic therapy", section on 'Continuous versus intermittent androgen deprivation'.)

Timing of ADT

Symptomatic metastases — For patients with symptomatic metastases, androgen deprivation therapy should be initiated promptly, both to palliate symptoms and to prevent severe complications (eg, pathologic fractures, spinal cord compression) [5].

Asymptomatic metastases — Treatment for metastatic prostate cancer is not curative and treatment-related side effects can adversely affect quality of life. Therefore, a major question remains for asymptomatic patients whether to start therapy as soon as metastatic disease is diagnosed or whether to delay treatment until significant symptoms are present.

The optimal timing for therapeutic intervention has been addressed in a number of randomized trials. However, the interpretation of these trials is limited by their heterogeneous patient populations, which often included large numbers of patients with locally advanced disease but without evidence of disseminated metastases. Furthermore, some of the patients in these trials did not receive deferred treatment as originally planned.

A 2007 meta-analysis combined the results from 3065 patients in four randomized trials [3]. In this analysis, early ADT was associated with a statistically significant decrease in prostate cancer-related deaths (relative risk [RR] 0.84; 95% CI 0.77-0.92), although there was no significant benefit in overall survival (RR 0.98; 95% CI 0.95-1.01).

The completed trials did not incorporate prognostic factors that are associated with disease progression, such as PSA doubling time, Gleason score, and PSA response to ADT. Additional studies will be required to determine if there are subsets of patients with asymptomatic metastases in whom therapy initiation can be deferred.

We suggest that early treatment be used to reduce the morbidity from potential complications of untreated disease (eg, ureteral obstruction, pathologic fractures, spinal cord compression, urethral obstruction, extraskeletal metastases).

Rising serum PSA — The factors affecting the optimal timing of treatment for men whose only manifestation of disseminated prostate cancer is an elevated serum PSA are discussed separately. (See "Rising serum PSA after treatment for localized prostate cancer: Systemic therapy", section on 'When to initiate ADT'.)

Other hormonal approaches — Other hormonal approaches have been studied as a means to achieve similar anti-tumor efficacy in hormone sensitive patients without the toxicities associated with androgen deprivation therapy (ADT). These approaches either have not proven equivalent to ADT or remain experimental, and ADT remains the standard of care.

Antiandrogen monotherapy — A meta-analysis of eight trials that compared antiandrogens alone with medical or surgical castration found a trend toward shorter overall survival with antiandrogen monotherapy compared with castration that approached, but did not reach, statistical significance (HR 1.22, 95% CI 0.99-1.40) [24]. Antiandrogens, particularly bicalutamide, have been extensively studied. Based upon extensive clinical trials, the use of these agents is generally restricted to combination with GnRH analogs as a component of combined androgen blockade or for secondary endocrine therapy in patients with castration resistant disease. (See 'Combined androgen blockade with antiandrogens' above and "Secondary endocrine therapies for castration resistant prostate cancer", section on 'Antiandrogens'.)

Enzalutamide — Enzalutamide binds to the androgen receptor and blocks the intracellular effects of androgen; randomized trials have established its efficacy in patients with advanced castration resistant disease. (See "Castration resistant prostate cancer: Treatments targeting the androgen

pathway", section on 'Enzalutamide'.)

The activity of enzalutamide as initial therapy was assessed in a phase II study in 67 men with hormone sensitive disease that would normally be treated with ADT [42]. At week 25, 62 patients (93 percent) achieved a ≥80 percent decrease in serum prostate specific antigen (PSA). The most common side effects were gynecomastia, fatigue, nipple pain, and hot flashes (36, 34, 19, and 18 percent, respectively). A determination of the ultimate duration of activity and the efficacy relative to standard ADT will require comparative clinical trials and longer follow-up. The use of enzalutamide in men with hormone sensitive prostate cancer remains experimental.

CHEMOHORMONAL THERAPY — Historically, androgen deprivation therapy (ADT) alone has been the standard of care for the initial treatment of men with metastatic castration sensitive disease. However, contemporary results have demonstrated a statistically significant and clinically meaningful overall survival benefit for chemohormonal therapy combining ADT with docetaxel chemotherapy, compared with ADT alone, in men with high volume metastatic castration sensitive prostate cancer. Thus, chemohormonal therapy is the preferred option for this patient subset for men who are candidates for docetaxel chemotherapy.

The most extensive data come from the CHAARTED trial, in which 790 men with previously untreated, castration sensitive metastatic prostate cancer were randomly assigned to ADT plus docetaxel (six cycles of 75 mg/m^2 given every three weeks) or to ADT alone [43]. Approximately 65 percent of patients had high volume disease, defined by visceral metastases and/or four or more bone metastases (including at least one bone metastasis beyond the pelvis or axial skeleton). The primary endpoint of the trial was overall survival.

Preliminary results were presented at the 2014 ASCO meeting. At a median follow-up of 29 months, overall survival for the entire study population was significantly increased with chemohormonal therapy compared with ADT alone (median 58 versus 44 months, hazard ratio [HR] 0.61, 95% CI 0.47-0.80). In men with high volume disease, overall survival was significantly increased (median 49 versus 32 months, HR 0.60, 95% CI 0.45-0.81). In men with low volume disease, a similar overall survival benefit was observed, but there were too few deaths to be meaningful and additional follow-up will be required (median not reached for either treatment regimen, HR 0.63, 95% CI 0.34-1.17, p = 0.14).

Secondary trial endpoints also showed a benefit from chemohormonal therapy compared with ADT alone. Achieving a serum PSA <0.2 ng/mL was significantly more frequent at both 6 and 12 months with chemohormonal therapy compared with ADT alone (28 versus 14 percent, and 23 versus 12 percent, respectively). The median time to clinical progression was also significantly longer with chemohormonal therapy (33 versus 20 months, HR 0.49, 95% CI 0.37-0.65).

Additional information will be required to fully interpret the results of this trial, including longer follow-up to assess potential delayed toxicity associated with this approach. Furthermore, the trial was conducted prior to the availability of some of the newer therapeutic approaches, and the relative value of aggressive initial therapy in this context will require ongoing evaluation.

Somewhat different results were observed in a smaller trial, in which 385 men with metastatic prostate cancer were randomly assigned to ADT (either a gonadotropin releasing hormone [GnRH] agonist or orchiectomy) plus docetaxel (75 mg/m^2 every three weeks for up to nine cycles) or to ADT alone [44]. At a median follow-up of 50 months, there was a statistically significant increase in biochemical progression-free survival. There was no statistically significant increase in overall survival with the combination compared with ADT alone (median 59 versus 54 months, HR 1.01, 95% CI 0.75-1.36). However, there were substantial differences in the patient population, with approximately 77 percent of patients classified as having low or intermediate risk disease.

In the ongoing STAMPEDE trial (NCT00268476), multiple combination regimens, including docetaxel plus ADT, are being compared with ADT alone. No results are currently available.

PREVENTION OF OSTEOPOROSIS — Androgen deprivation therapy (ADT), with either medical or surgical orchiectomy, increases bone turnover, decreases bone mineral density, and increases the risk of clinical bone fractures in men with prostate cancer [45-47]. (See "Side effects of androgen deprivation therapy", section on 'Osteoporosis and bone fractures'.)

We recommend dietary calcium intake (food and supplements) of 1000 to 1200 mg daily and supplemental vitamin D 800 to 1000 international units daily for all men receiving ADT. We also recommend weight bearing exercise, decreased alcohol consumption, and smoking cessation [48-51]. Estimates of fracture risk using the FRAX algorithm (www.shef.ac.uk/FRAX/) with or without bone density measurements may provide guidance in consideration of medical therapies to prevent fracture. (See "Side effects of androgen deprivation therapy", section on 'Lifestyle modification'.)

Baseline and periodic measurement of bone density are also useful in detecting early evidence of osteoporosis [5].

The roles of concurrent therapy with an osteoclast inhibitor (denosumab, bisphosphonates) in men with and without bone metastases are discussed separately. (See "Bone metastases in advanced prostate cancer: Management", section on 'Osteoclast inhibition' and "Side effects of androgen deprivation therapy", section on 'Prevention'.)

SIDE EFFECTS OF ANDROGEN DEPRIVATION THERAPY — The side effects of androgen deprivation therapy, including prevention and management, are discussed in detail separately. (See "Side effects of androgen deprivation therapy".)

SURVEILLANCE DURING TREATMENT — Surveillance strategies during treatment for disseminated prostate cancer are discussed separately. (See "Follow-up surveillance during and after treatment for prostate cancer", section on 'Metastatic prostate cancer'.)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also

locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Beyond the Basics topic (see "Patient information: Treatment for advanced prostate cancer (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Androgen deprivation therapy (ADT) (ie, lowering the serum testosterone level to castrate levels) is an integral component of the initial treatment of men with castration sensitive metastatic prostate cancer. (See 'Androgen deprivation therapy' above.)
  - For men with asymptomatic metastatic disease, we suggest early rather than delayed treatment (**Grade 2B**). Although early treatment may not improve overall survival, this approach is associated with improved progression-free survival. (See 'Asymptomatic metastases' above.)
  - For men with low volume disease (ie, no visceral metastases and less than four bone metastases), we suggest treatment with ADT alone rather than chemohormonal therapy (**Grade 2B**). (See 'Androgen deprivation therapy' above.)
  - For men with high volume disease (visceral metastases and/or four or more bone metastases), we recommend chemohormonal therapy combining ADT with docetaxel chemotherapy rather than ADT alone (**Grade 1B**). (See 'Chemohormonal therapy' above.)
- ADT can be accomplished either by surgical orchiectomy (castration) or medical orchiectomy (using either a gonadotropin releasing hormone [GnRH] agonist or a GnRH antagonist). Newer modalities that have been demonstrated to prolong survival in men with metastatic disease have only been evaluated in men who have progressed after ADT (ie, castration resistant disease) and are not indicated in this setting (table 1). (See 'Surgical orchiectomy' above and 'Medical orchiectomy' above and "Overview of the treatment of disseminated prostate cancer".)
  - For patients managed with medical orchiectomy, we suggest using an antiandrogen for two to four weeks during GnRH agonist initiation to prevent a disease flare due to the transient increase in testosterone levels (**Grade 2B**).Use of the GnRH antagonist degarelix is an alternative. (See 'Initiation of ADT' above and 'GnRH antagonists' above.)
    - After the initial treatment induction, we suggest monotherapy using a GnRH agonist rather than combined androgen blockade with a GnRH agonist plus an antiandrogen (**Grade 2B**). Long-term combined androgen blockade may have a modest survival benefit compared with GnRH agonist monotherapy, but combined androgen blockade has more side effects and greater cost. (See 'Combined androgen blockade with antiandrogens' above.)
    - We recommend continuous therapy rather than intermittent androgen deprivation (**Grade 1B**). (See 'Intermittent androgen deprivation' above.)
  - Because of the increased bone turnover and decreased bone mineral density, dietary calcium intake (food and supplements) of 1000 to 1200 mg daily and supplemental vitamin D 800 to 1000 international units daily, as well as lifestyle modifications (weight bearing exercise, decreased alcohol consumption, smoking discontinuation), are indicated for all men beginning ADT and for those who undergo surgical orchiectomy. (See "Side effects of androgen deprivation therapy", section on 'Prevention'.)
- For men whose only evidence of disseminated disease is an elevated or rising serum PSA, issues regarding the optimal timing of initiating treatment and the use of continuous versus intermittent ADT are discussed separately. (See "Rising serum PSA after treatment for localized prostate cancer: Systemic therapy".)

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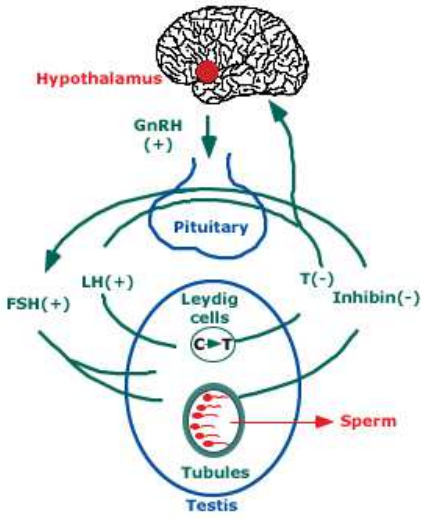
Topic 6951 Version 26.0

GRAPHICS

Hypothalamic-pituitary-testicular axis



Schematic representation of the hypothalamic-pituitary-testicular axis shows the site of action of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in the testes. Testosterone (T) and inhibin are produced by the testes. Testosterone has a negative feedback on the hypothalamus and LH production, while inhibin has a negative feedback on FSH production.

C: cholesterol; GnRH: gonadotropin releasing hormone.

Adapted from Griffin JE, Wilson JD. In: Metabolic Control and Disease, 8th ed, Bondy PK, Rosenberg LE (Eds), Saunders, Philadelphia 1980. p. 1535.

Graphic 50484 Version 2.0

Therapies for castration resistant prostate cancer (CRPC)

Approach	Indications	Route, schedule	Steroids	Symptoms, disease burden	Contraindications	PSA response to treatment	Median overall survival benefit
Abiraterone	Metastatic CRPC	Oral, daily	Required	–	Severe liver dysfunction; hypokalemia; heart failure	Yes	Post docetaxel: 4.6 mos. [1] Chemotherapy naive: 5.2 mos. [2]
Enzalutamide	Metastatic CRPC	Oral, daily	Not required	–	Seizures	Yes	4.8 mos. [3]
Sipuleucel-T	Pre or post docetaxel	IV, every 2 weeks x 3 doses	Possibly contraindicated	Asymptomatic or minimally symptomatic	Steroids; narcotics for cancer-related pain; GM-CSF; liver metastases	No	4.1 mos. [4]
Docetaxel	Metastatic CRPC	IV, every 3 weeks	Required	–	Moderate liver dysfunction; cytopenias	Yes	2.5 mos. [5]
Cabazitaxel	Post docetaxel	IV, every 3 weeks	Required	–	Moderate liver dysfunction; cytopenias	Yes	2.4 mos. [6]
Radium-223	Symptomatic bone metastases with no known visceral metastases	IV, every 4 weeks	Not required	Symptomatic bone metastases	Visceral metastases	Not reported	3.6 mos. [7]

* Median survival not reached for abiraterone; hazard ratio 0.75.

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Graphic 85716 Version 14.0

Disclosures

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