Chapter 64: Prostate Cancer

INTRODUCTION

- *Prostate cancer* is a malignant neoplasm that arises from the prostate gland. Prostate cancer has an indolent course; localized prostate cancer is curable by surgery or radiation therapy, but advanced prostate cancer is not yet curable.

PATHOPHYSIOLOGY

- The normal prostate is composed of acinar secretory cells that are altered when invaded by cancer. The major pathologic cell type is adenocarcinoma (>95% of cases).
- Prostate cancer can be graded. Well-differentiated tumors grow slowly, whereas poorly differentiated tumors grow rapidly and have a poor prognosis.
- Metastatic spread can occur by local extension, lymphatic drainage, or hematogenous dissemination. Skeletal metastases from hematogenous spread are the most common sites of distant spread. The lung, liver, brain, and adrenal glands are the most common sites of visceral involvement, but these organs are not usually involved initially.
- Hormonal regulation of androgen synthesis is mediated through a series of biochemical interactions between the hypothalamus, pituitary, adrenal glands, and testes (**Figure 64-1**).
- The testes and the adrenal glands are the major sources of androgens, specifically dihydrotestosterone (DHT).
- Luteinizing hormone–releasing hormone (LHRH) from the hypothalamus stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland.
- LH complexes with receptors on the Leydig cell testicular membrane, stimulating the production of testosterone and small amounts of estrogen.
- FSH acts on testicular Sertoli cells to promote maturation of LH receptors and produce an androgen-binding protein.
- Circulating testosterone and estradiol influence the synthesis of LHRH, LH, and FSH by a negative-feedback loop at the hypothalamic and pituitary level.

FIGURE 64-1

Hormonal regulation of the prostate gland.

(ACTH, adrenocorticotropic hormone; DHT, dihydrotestosterone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; LHRH, luteinizing hormone–releasing hormone; mRNA, messenger RNA; PROL, prolactin; R, receptor.)

image

CHEMOPREVENTION

- The use of 5-α-reductase inhibitors, **finasteride** and **dutasteride**, to prevent prostate cancer has been debated for more than a decade. Current guidelines do not recommend the use of these agents for prostate cancer chemoprevention.

SCREENING

- Screening recommendations for prostate cancer have changed, and digital rectal examination (DRE) and prostate-specific antigen (PSA) are no longer recommended for patients without a discussion with their clinician about risks versus benefits. The American Urologic Association does not recommend routine screening in men between the ages of 40 and 54 years of average risk. They recommend that men aged 55–69 years discuss the risks and benefits of prostate cancer screening. Men who elect to have screening should do so no more than every 2 years; a recent study suggests that screening every 5 years may be adequate.
- PSA is a glycoprotein produced and secreted by prostate epithelial cells. Acute urinary retention, acute prostatitis, and BPH influence PSA, thereby limiting the usefulness of PSA alone for early detection, but it is a useful marker for monitoring response to therapy.

CLINICAL PRESENTATION

- Localized prostate cancer is usually asymptomatic.
- Locally invasive prostate cancer is associated with ureteral dysfunction or impingement, such as alterations in micturition (eg, urinary frequency, hesitancy, and dribbling), and impotence.
- Advanced disease commonly presents with back pain and stiffness due to osseous metastases. Untreated spinal cord lesions can lead to cord compression. Lower extremity edema can occur as a result of lymphatic obstruction. Anemia and weight loss are nonspecific signs of advanced disease.

TREATMENT

- Goals of Treatment: In early-stage prostate cancer, the goal is to minimize morbidity and mortality. Surgery and radiation therapy are curative but also associated with significant morbidity and mortality. In advanced prostate cancer, treatment focuses on providing symptom relief and maintaining quality of life.

General Approach

- Initial treatment depends on disease stage, Gleason score, presence of symptoms, and patient's life expectancy. The most appropriate therapy for early-stage prostate cancer is unknown. See **Table 64-1** for management recommendations based on risk of recurrence.
- Initial treatment modality for advanced prostate cancer is androgen ablation (eg, orchiectomy or LHRH agonists with or without antiandrogens). After disease progression, secondary hormonal manipulations, cytotoxic chemotherapy, and supportive care are used.

TABLE 64-1

Initial Management of Prostate Cancer Based on Expected Survival and Recurrence Risk

Recurrence Risk	Expected Survival (Years)	Initial Therapy
Very low		
T_{1c}, Gleason score less than 6 and PSA less than 10 ng/mL (mcg/L)	<20	Observation
T_{1c}, Gleason score less than 6 and PSA less than 10 ng/mL (mcg/L)	20 or more	Observation or Radical prostatectomy with or without pelvic lymph node dissection or

		Radiation therapy
Low		
T_1–T_{2a} and Gleason and PSA less than 10 ng/mL (mcg/L) and <5% tumor in the specimen	10 or more	Observation or Radical prostatectomy with or without pelvic lymph node dissection or radiation therapy
	<10	Observation
Intermediate		
T_{2b}–T_{2c} or Gleason 7 or PSA 10–20 ng/mL (mcg/L)	10 or more	Observation or Radical prostatectomy with pelvic lymph node dissection or Radiation therapy with or without 4–6 months of neoadjuvant ADT with or without brachytherapy
T_{2b}–T_{2c} or Gleason 7 or PSA 10–20 ng/mL (mcg/L)	10 or more	Radical prostatectomy with pelvic lymph node dissection or Radiation therapy with or without 4–6 months of neoadjuvant ADT with or without brachytherapy
High		
T_{3a}, Gleason 8–10, PSA >20 ng/mL (mcg/L)	5 years or more	Radiation therapy and ADT[a] (2–3 years) with or without brachytherapy or Radical prostatectomy and pelvic lymph node dissection
Very high		
T_{3b}–T_4 or Gleason pattern 5 or >4 cores with Gleason score 8–10		Radiation therapy and ADT (2–3 years) with or without brachytherapy or Radical prostatectomy and pelvic lymph node dissection or ADT
Very high		
Any T, N_1		ADT (2–3 years) with or without abiraterone and prednisone or Radiation therapy and ADT (2–3 years) with or without abiraterone and prednisone (or methylprednisolone)
Any T, Any N, M_1		Orchiectomy or LHRH agonist[b] with or without an antiandrogen or

		LHRH antagonist or Observation

[a]Androgen deprivation therapy to achieve serum testosterone levels <50 ng/dL (1.7 nmol/L).

[b]LHRH agonist, medical castration, or surgical castration is equivalent.

ADT, androgen-deprivation therapy; LHRH, luteinizing hormone–releasing hormone; PSA, prostate-specific antigen.

Nonpharmacologic Therapy

Observation

- Observation or watchful waiting involves monitoring the course of disease and initiating treatment if the cancer progresses. PSA and DRE are performed every 6 months.
- Advantages include avoiding adverse effects of definitive therapies and minimizing risk of unnecessary therapies. The major disadvantage is the risk of cancer progression requiring more intense therapy.

Surgery and Radiation Therapy

- Bilateral orchiectomy rapidly reduces circulating androgens to castrate levels. Many patients are not surgical candidates due to advanced age, and other patients find this procedure psychologically unacceptable. Orchiectomy is the preferred initial treatment for patients with impending spinal cord compression or ureteral obstruction.
- Radical prostatectomy and radiation therapy are potentially curative therapies but are associated with complications that must be weighed against expected benefit. Consequently, many patients postpone therapy until symptoms develop.
- Complications of radical prostatectomy include blood loss, stricture formation, incontinence, lymphocele, fistula formation, anesthetic risk, and impotence. Nerve-sparing techniques facilitate return of sexual potency after prostatectomy.
- Acute complications of radiation therapy include cystitis, proctitis, hematuria, urinary retention, penoscrotal edema, and impotence.
- Chronic complications of radiation therapy include proctitis, diarrhea, cystitis, enteritis, impotence, urethral stricture, and incontinence.

Pharmacologic Therapy

Drug Treatments of First Choice

Luteinizing Hormone–Releasing Hormone Agonists

- LHRH agonists are a reversible method of androgen ablation and are as effective as orchiectomy.
- There are no comparative trials of LHRH agonists, so the choice is usually based on cost and patient and physician preference for a dosing schedule (**Table 64-2**). **Leuprolide acetate**, **leuprolide depot**, **leuprolide implant**, **triptorelin depot**, **triptorelin implant**, and **goserelin acetate implant** are currently available. Dosing intervals range from once monthly to every 6 months. Leuprolide implant is a mini-osmotic pump that delivers daily doses for 1 year. Testosterone castration levels are achieved in 28 days with leuprolide.
- The most common adverse effects of LHRH agonists include disease flare-up during the first week of therapy (eg, increased bone pain or urinary symptoms), hot flashes, erectile impotence, decreased libido, and injection-site reactions. Use of an antiandrogen (eg, **flutamide**, **bicalutamide**, or **nilutamide**) prior to initiation of LHRH therapy and for 2–4 weeks after is a strategy to minimize initial tumor flare.

- Decreases in bone mineral density complicate androgen deprivation therapy (ADT), resulting in increased risk of osteoporosis, osteopenia, and skeletal fractures. Calcium and vitamin D supplements and a baseline bone mineral density are recommended. Consider administering an antiresorptive agent (eg, **denosumab** or **zoledronic acid**) to reduce the risk of skeletal-related events.
- Screen patients receiving ADT for cardiovascular disease and diabetes due to increased risk of metabolic effects.

TABLE 64-2

Hormonal Therapies for Prostate Cancer

Drug (Brand Name)	Usual Dose	Toxicities	Hepatic/Renal Adjustments	Monitoring Parameters	Drug Interactions	Administration
First-Generation Antiandrogens						
Flutamide (Eulexin)	750 mg/day	Gynecomastia Hot flashes GI disturbances (diarrhea) Loss of libido LFT abnormalities Breast tenderness Methemoglobinemia	Contraindicated in patients with hepatic impairment No dosage adjustment necessary in chronic renal impairment	Monitor serum transaminases prior to start of therapy and monthly for the first 4 months, then periodically thereafter Monitor for tumor reduction, testosterone/estrogen, and alkaline phosphatase serum levels	Substrate of CYP1A2 and CYP3A4	Administered orally in three divided doses; capsule may be opened into applesauce, pudding, or other soft foods
Bicalutamide (Casodex)	50 mg/day (up to 150 mg/day—unlabeled use)	Gynecomastia Hot flashes GI disturbances (diarrhea) Decreased libido LFT abnormalities Breast tenderness	Discontinue if ALT >2 times upper limit of normal or patient develops jaundice	Monitor serum transaminases prior to start of therapy and monthly for the first 4 months, then periodically thereafter Periodic monitoring of CBC, EKG, echocardiograms, serum testosterone, luteinizing hormone, and PSA	Inhibits CYP3A4 May increase the concentration of vitamin K antagonists	May be taken with or without food
Nilutamide (Nilandron)	300 mg/day for first month then 150 mg/day	Gynecomastia Hot flashes GI disturbances (constipation) LFT abnormalities Breast tenderness Visual disturbances (impaired dark adaptation) Alcohol intolerance Interstitial pneumonitis	Contraindicated in patients with hepatic impairment Discontinue if ALT >2 times upper limit of normal or patient develops jaundice	Monitor serum transaminases prior to start of therapy and monthly for the first 4 months, then periodically thereafter Chest x-ray at baseline and consider pulmonary function testing (at baseline)	Substrate of CYP2C19 and weak inhibitor of CYP2C19	May be taken with or without food

Second-Generation Antiandrogens						
Apalutamide (Erleada)	240 mg/day	GI disturbances (diarrhea, nausea) Hot flashes Fatigue Hypertension Rash Decreased weight Falls and fractures Peripheral edema Seizures	No adjustment necessary for renal or hepatic impairment	CBC baseline and periodically LFTs baseline and periodically	Strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9	May be taken with or without food
Enzalutamide (Xtandi)	160 mg/day	GI disturbances (diarrhea) Musculoskeletal disorders (back pain, arthralgias, muscle pain, weakness) Asthenia Peripheral edema CNS (headache, dizziness) Seizures LFT abnormalities	No adjustment necessary for renal or hepatic impairment	CBC baseline and periodically LFTs baseline and periodically	Strong CYP3A4 and moderate CYP2C9 and CYP2C19 inducer; avoid CYP3A4, CYP2C9, and CYP2C19 sensitive substrates. CYP2C8 substrate, avoid strong inducers and inhibitors of CYP2C8. If vitamin K antagonists are necessary, conduct additional INR monitoring	May be taken with or without food
Darolutamide (Nubeqa)	1200 mg/day	Fatigue GI disturbances (diarrhea, constipation, nausea) Rash Musculoskeletal disorders (back pain, arthralgias, pain in an extremity) Falls, including accidents/bone fractures Hypertension Seizures	For moderate hepatic impairment or severe renal impairment (not on dialysis): reduce dose to 600 mg/day	CBC baseline and periodically LFTs baseline and periodically	Breast cancer resistance protein (BCRP) transporter Inhibitor Darolutamide inhibits OATP1B1 and OATP1B3	Take with food
Androgen Synthesis Inhibitor						
Abiraterone acetate (Zytiga)	1000 mg/day + prednisone 5 mg BID	GI disturbances (diarrhea) Edema Hypokalemia Hypophosphatemia	250 mg daily for Child–Pugh Class B; avoid use in Child–Pugh Class C	Monitor serum transaminases prior to start of therapy, every 2 weeks for 3 months, then monthly thereafter	Substrate of CYP3A4. Use with caution with CYP3A4 inhibitors and inducers Inhibits CYP1A2, CYP2C19,	Take on an empty stomach, at least 1 hour before or 2 hours after food

		LFT abnormalities Hypertriglyceridemia	Withhold treatment if LFTs >5 times the ULN or bilirubin >3 ULN	Monitor for signs and symptoms of adrenocorticoid insufficiency; monthly for hypertension, hypokalemia, and fluid retention	CYP2C8, CYP2C9, CYP2D6, CYP3A4, and P-glycoprotein Use sensitive substrates with caution	
Luteinizing-Hormone Agonists						
Leuprolide (Lupron)	7.5 mg IM every month 22.5 mg IM every 3 months 30 mg IM every 4 months 45 mg IM every 6 months	Hot flashes Decreased libido Gynecomastia Osteoporosis Fatigue Weight gain	No adjustment necessary for renal or hepatic impairment	Serum testosterone ~4 weeks after initiation, PSA, blood glucose, and A1C prior to initiation and periodically thereafter	May diminish the effects of antidiabetic agents	Vary injection site
Goserelin (Zoladex)	3.6 mg SQ implant every month 10.8 mg SQ implant every 3 months	Hot flashes Decreased libido Gynecomastia Osteoporosis Fatigue Weight gain	No adjustment necessary for renal or hepatic impairment	Monitor bone mineral density, serum calcium, and cholesterol/lipids	May diminish the effects of antidiabetic agents	Vary injection site
Triptorelin (Trelstar)	3.75 mg IM every month 11.25 mg IM every 3 months 22.5 mg IM every 6 months	Hot flashes Decreased libido Gynecomastia Osteoporosis Fatigue Weight gain	No adjustment necessary for renal or hepatic impairment	Monitor serum testosterone levels and PSA	May diminish the effects of antidiabetic agents	Vary injection site
Gonadotropin-Releasing Hormone Antagonists						
Degarelix (Firmagon)	240 mg SQ loading dose 80 mg SQ every 28 days	Hot flashes Decreased libido Gynecomastia Osteoporosis Fatigue Weight gain	Use with caution with CL_{cr} <50 mL/min (0.83 mL/sec) Do not use in	PSA periodically, serum testosterone monthly until castration achieved then every other month, LFTs at baseline in addition to serum	Use with caution with agents that may increase QTc interval	Vary injection site

	(following 28 days after loading dose)		patients with severe hepatic impairment	electrolytes and bone mineral density		

ALT, alanine aminotransferase; BID, twice daily; CBC, complete blood count; CL_{cr}, creatinine clearance; CNS, central nervous system; CYP, cytochrome P450; EKG, electrocardiogram; GI, gastrointestinal; IM, intramuscular injection; INR, international normalized ratio; LFT, liver function test; PSA, prostate-specific antigen; SQ, subcutaneous injection; ULN, upper limit of normal.

Gonadotropin-Releasing Hormone Antagonists

- The gonadotropin-releasing hormone (GnRH) antagonist **degarelix** binds reversibly to GnRH receptors in the pituitary gland, reducing the production of testosterone to castrate levels in 7 days or less. A major advantage of degarelix over LHRH agonists is the lack of tumor flare.
- Degarelix is administered as a subcutaneous injection every 28 days. Injection site reactions are the most frequently reported adverse effects and include pain, erythema, swelling, induration, and nodules. Osteoporosis may develop, and calcium and vitamin D supplementation should be considered.

Antiandrogens

- Monotherapy with flutamide, bicalutamide, and nilutamide is no longer recommended due to decreased efficacy as compared with patients treated with LHRH agonist therapy. Antiandrogens are indicated for advanced prostate cancer only when combined with an LHRH agonist (flutamide and bicalutamide]) or orchiectomy (nilutamide). In combination, antiandrogens can reduce the LHRH agonist–induced flare.
- **Apalutamide**, **enzalutamide**, and **darolutamide** are second-generation antiandrogens. Apalalutamide was initially approved in the nonmetastatic castration naive patient population but has since been approved for castrate-resistant prostate cancer (CRPC). Enzalutamide may be used in the first-line setting to delay the initiation of chemotherapy in both nonmetastatic and metastatic disease
- Adverse effects of antiandrogens are summarized in **Table 64-2**.

Combined Androgen Blockade

- The role of combined androgen blockade (CAB), also referred to as *maximal androgen deprivation* or *total androgen blockade*, continues to be evaluated. The combination of LHRH agonists or orchiectomy with antiandrogens is the CAB approach most extensively studied.
- Some clinicians consider CAB to be the initial hormone therapy of choice for newly diagnosed patients because the major benefit is seen in patients with minimal disease. Some argue that treatment should not be delayed because combined androgen deprivation trials demonstrate a survival advantage for young patients with good performance status and minimal disease who were initially treated with hormone therapy.

Alternative Drug Treatments

- Selection of salvage therapy depends on what was used as initial therapy. Radiotherapy can be used after failed radical prostatectomy. Androgen ablation can be used after progression of disease after radiation therapy or radical prostatectomy.
- An antiandrogen or orchiectomy may be indicated if testosterone levels are not suppressed (ie, >20 ng/dL [0.7 nmol/L]) after initial LHRH agonist therapy. If testosterone levels are suppressed, the disease is considered androgen-independent and palliative androgen-independent salvage therapy can be used.
- Androgen withdrawal should be attempted if initial therapy consists of CAB with an LHRH agonist and antiandrogen. Mutations of the androgen receptor may allow antiandrogens to become agonists. Androgen withdrawal produces responses lasting 3–14 months in up to 35% of patients.

- Androgen synthesis inhibitors provide symptomatic but brief relief in approximately 50% of patients. **Aminoglutethimide** causes adverse effects in 50% of patients, such as lethargy, ataxia, dizziness, and self-limiting rash. The adverse effects of **ketoconazole** include GI intolerance, transient increases in liver and renal function tests, and hypoadrenalism. **Abiraterone** targets CYP17A1, resulting in decreased circulating levels of testosterone (**Table 64-2**). Review medication profiles for potential drug interactions because abiraterone is an inhibitor of CYP2D6.

Chemotherapy

- **Docetaxel,** 75 mg/m^2 every 3 weeks, combined with **prednisone,** 5 mg twice daily, improves survival in CRPC. The most common adverse events include nausea, alopecia, and myelosuppression (**Table 64-3**).

- **Cabazitaxel** 25 mg/m^2 every 3 weeks with prednisone 10 mg daily significantly improves progression-free and overall survival in patients previously treated with docetaxel and prednisone. Neutropenia, febrile neutropenia, neuropathy, and diarrhea are the most significant toxicities.

TABLE 64-3

Chemotherapy and Immunotherapy for Prostate Cancer

Drug (Brand Name)	Usual Dose	Toxicities	Hepatic/Renal Adjustments	Monitoring Parameters	Drug Interactions	Administration
Antimicrotubule Agents						
Docetaxel (Taxotere)	75 mg/m^2 IV every 3 weeks	Fluid retention, alopecia, mucositis, myelosuppression, hypersensitivity	Do not administer if AST/ALT >1.5 times the upper limit of normal and alkaline phosphatase >2.5 times the upper limit of normal	CBC with differential, LFTs, bilirubin, alkaline phosphatase, renal function Monitor for hypersensitivity reactions	Avoid concomitant use of CYP3A4 inhibitors	Administer IV infusion over 1 hour. Premedication with corticosteroids for 3 days beginning the day before
Cabazitaxel (Jevtana)	25 mg/m^2 IV every 3 weeks	Fluid retention, constipation, mucositis, myelosuppression, hypersensitivity	Discontinue if ALT >2 times upper limit of normal or patient develops jaundice	CBC weekly during the first cycle, then prior to each treatment Monitor for hypersensitivity	Avoid concomitant use of CYP3A4 inducers and inhibitors	Administer IV infusion over 1 hour
Immunotherapy						
Sipuleucel-T (Provenge)	Each injection contains >50 million autologous CD54+ cells (obtained through leukapheresis) activated with PAP-GM-CSF Dose is given ~ every 2 weeks for 3 total doses	Hypersensitivity, chills, fatigue, fever, headache, myalgias	No dosage adjustment necessary for renal or hepatic dysfunction	No specific laboratory monitoring recommended	Immunosuppressants may decrease the therapeutic effects of sipuleucel-T	Administer IV infusion over 1 hour Observe the patient for 30 minutes after completion of the infusion Premedicate with acetaminophen and an antihistamine 30 minutes prior to administration

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; CYP, cytochrome P450; LFT, liver function test; PAP-GM-CSF, prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor.

Immunotherapy

- **Sipuleucel-T** is a novel autologous cellular immunotherapy indicated for asymptomatic or minimally symptomatic metastatic CRPC. Use is controversial because trials have not been done to compare it to standard second-line hormonal interventions.

Nuclear Medicine

- Radium-223, an alpha emitter, can be used in first-, second-, or third-line therapy in patients with metastatic CRPC with symptomatic primary bone metastases. It has not been approved for use with concomitant chemotherapy.
- Radium-223 improved survival, pain-related outcomes, quality of life and decreased opioid needs. The most common adverse effects include nausea, diarrhea, vomiting, peripheral edema, and bone marrow suppression.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor primary tumor size, involved lymph nodes, and tumor marker response such as PSA with definitive, curative therapy. PSA level is checked every 6 months for the first 5 years, then annually.
- With metastatic disease, clinical benefit can be documented by evaluating performance status, weight, quality of life, analgesic requirements, and PSA or DRE at 3-month intervals.

See Chapter 148, Prostate Cancer, authored by LeAnn B. Norris, for a more detailed discussion of this topic.