Advanced Oncology Certified Nurse Practitioner

REVIEW COURSE 2024

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Endocrine (Hormone) Therapy in Cancer Treatment

OBJECTIVES

- Describe the mechanisms of action for endocrine therapy for select tumors
- Identify classifications and associated side effects and health risks of endocrine therapy for prostate and breast cancer
- Discuss prevention and treatment strategies for select side effects of endocrine therapy

Systemic Treatments for Cancer

Chemotherapy		Targeted Therapy		
		Endocrine Therapy	Molecular Targeted	Immuno Targeted Therapy
Target:	Fast growing cells (both cancer cells and certain populations of normal cells)	Tumors cells that express hormone receptors & thrive in a hormonal environment	Gene/protein molecules and pathways that cancer cells use to proliferate, metastasize and avoid apoptosis	Cells and pathways of the Immune system
Based on:	Principles of cell kinetics and cell cycle	Hormonally driven tumors via cell signaling e.g. prostate, breast, ovarian cancers	Gene mutations specific to patient's cancer that cause dysregulated cell signaling	Theory of immunosurveillance and immune system manipulation

Use of Hormones to Treat Cancer

Role of endocrine therapy is well established in:

- Prostate cancer (90% are androgen drive initially)
- Estrogen receptor/Progesterone receptor positive breast cancer (70-75% estrogen driven) $\rightarrow$ also known as hormone+ (HR+)
- Limited use in select recurrent or metastatic ovarian and endometrial uterine cancers
- May also be used for adrenal, thyroid and androgen-sensitive salivary gland cancers

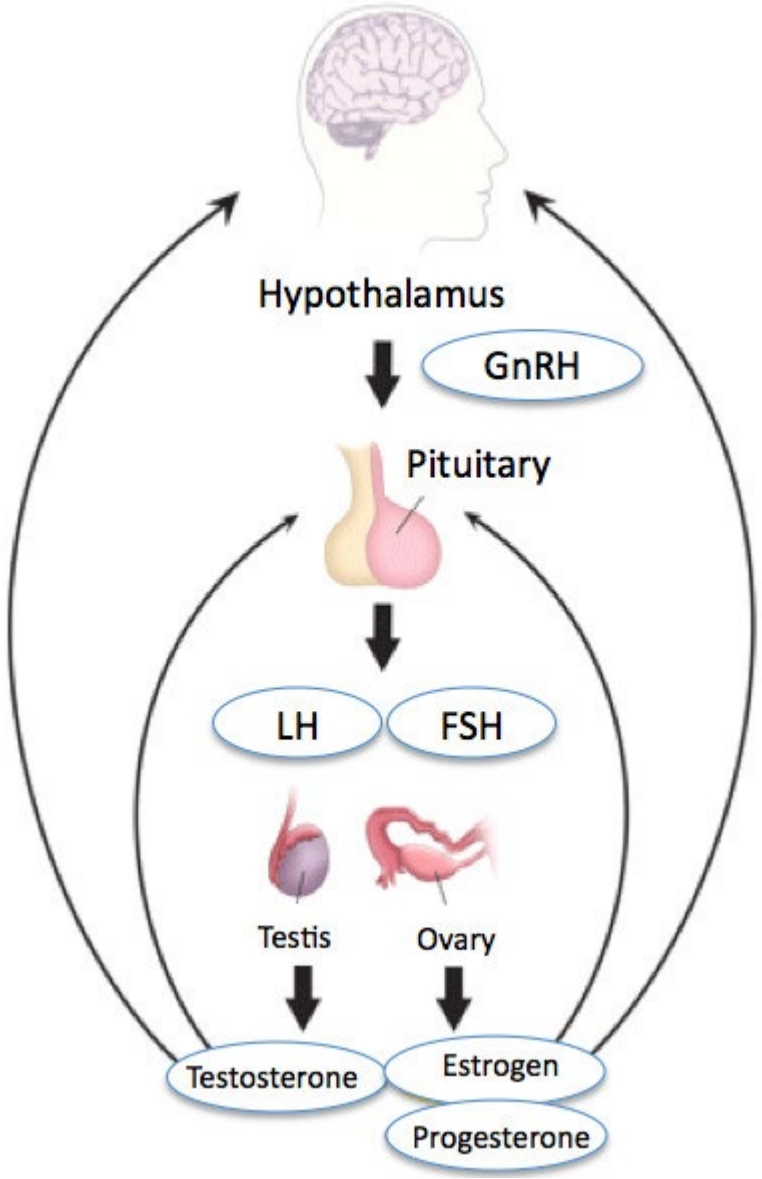
Hormone therapy can work by:

- stopping the production of a certain hormone
- blocking or degrading the hormone's receptors

Androgen Deprivation Therapy (ADT) in Prostate Cancer

Used in localized, locally advanced, and metastatic prostate cancer

- For localized disease → if PSA level starts to rise after surgery and/or radiation therapy, start ADT
- For localized disease and intermediate-risk or high- risk features → in combination with definitive RT
  - For intermediate-risk → at least 4 to 6 months of ADT
  - For high-risk → ADT for 2 to 3 years
- In metastatic disease if tumor androgen sensitive → use until castrate resistant
  - could be used alone, combination with chemo, or dual ADT blockade with a 2nd generation androgen targeted therapy



Hypothalamic-Pituitary-Gonadal Axis

Males

Surgical Castration

- Bilateral Orchiectomy

Medical (Chemical) Castration-

Androgen Deprivation Therapy ADT

androgen axis inhibitors

1. androgen synthesis inhibitors
2. androgen receptor inhibitors

Permission from Professor Peter Koopman, PhD, FAA http://www.dsdgenetics.org

Hormone Therapies: Prostate Cancer

Categories of Hormone Therapies	Examples
Luteinizing hormone-releasing hormone (LHRH) agonists • Stop testicular androgen production over several weeks & may have initial "androgen flare" • Concerned about SCC or ureteral obstruction with big tumor burden; initially give antiandrogen concurrently	Leuprolide (Lupron®) Goserelin (Zoladex ®) Histrelin (Vantas®) Triptorelin (Trelstar ®)
LHRH antagonists • Stop androgen production immediately; no "flare"	Degarelix (Firmagon®) injection Relugolix (Orgovyx®) po
Androgen Synthesis Inhibitor (CYP17 Inhibitors) • Stop adrenal androgen production; steroid needed to avoid ↓ K+, hypertension, & fluid retention	Abiraterone with methylprednisolone or prednisone (Zytiga®) (Yonsa®)
Antiandrogens • Compete with androgens for receptor site • Not used alone, in combination	1st- Nilutamde, Flutamide or Bicalutamide 2nd –Enzalutamide, Apalutamide, Darolutamide

Side Effects with Androgen Deprivation Therapy (ADT)

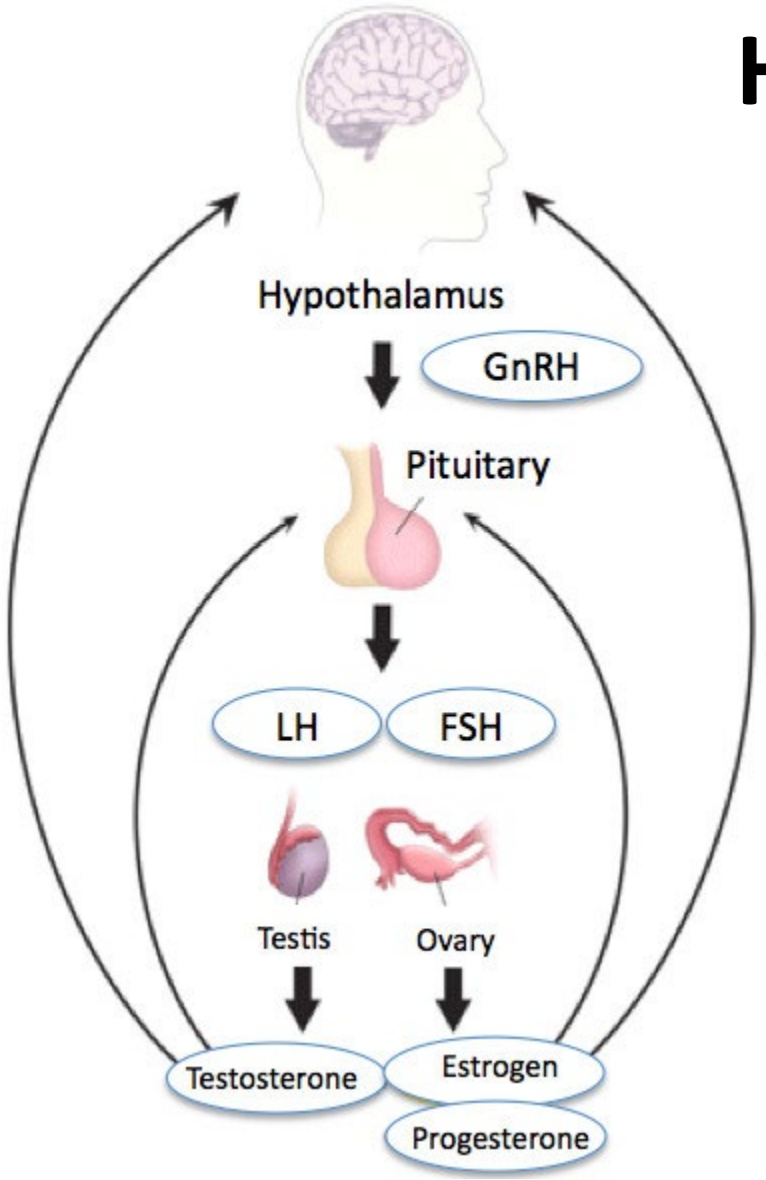
ADT Related Symptoms

- Vasomotor s/s (hot flashes/night sweats)
- Urinary complaints, sexual dysfunction (decreased libido, erectile dysfunction)
- Sleep disturbance, mood disturbance, depression,
- Cognitive dysfunction
- Arthralgias/myalgias, and fatigue
- Gynecomastia, ↓ penis and testicle size
- ↓ muscle mass (sarcopenia), ↑body fat
- Thinning of body hair

ADT Related Health Risks

- Acute renal injury
- Anemia
- Cardiovascular disease**
  - Prolongation of QT/QTc interval
- Diabetes mellitus (new onset)**
  - Reduced insulin sensitivity
- Osteoporosis/ bone fractures
- Venous thromboembolic disease

**Relugolix has much less effect on metabolic syndrome profile than LHRH agonists with a faster time to reduce androgen levels



Hypothalamic-Pituitary-Gonadal Axis

FEMALES

70-75% of breast cancers are estrogen driven → also known as hormone+ (HR+)

Ovarian ablation

- surgery- oophorectomy

Ovarian suppression

Use depends on hormone status (ER/PR) and Menopausal status

- Premenopausal (consider ovarian suppression/ablation)
- Postmenopausal

Permission from Professor Peter Koopman, PhD, FAA; http://www.dsdgenetics.org

Menopause – NCCN Definition

- Definition- permanent cessation of menses with permanent ↓ in ovarian estrogen synthesis
  - Usually a clinical diagnosis made after 12 months of amenorrhea
  - Natural menopause occurs between ages 42 and 58 years
- Menopausal status important → used to select endocrine therapy for breast cancer

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Criteria to determine menopause in breast cancer pts include any of the following:

- Prior bilateral oophorectomy
- Age ≥ 60 years
- Age <60 years with amenorrhea for ≥ 12 months in absence of prior chemotherapy, tamoxifen, toremifene or ovarian suppression AND estradiol (<30 pg/mL) and FSH (≥30 mIU/mL) in post-menopausal range
- Age < 60:
  - Chemotherapy- or tamoxifen – induced amenorrhea for ≥ 12 months with estradiol and FSH in post-menopausal range on <u>serial measurements</u>

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** Menopausal status cannot be determined if pt receiving ovarian function suppression

Hormone therapies: Breast Cancer

Categories of Hormone Therapies	Examples
Selective estrogen receptor modulators (SERMs) • selectively blocks estrogen receptors in breast tissue	Tamoxifen (Soltamox ®) (for treatment & prevention)
Selective estrogen receptor down regulators (SERDs) • block the effects of estrogen in breast tissue	Fulvestrant (Faslodex®)
Aromatase inhibitors (AI) • Inhibit the action of the enzyme aromatase, which converts androgens into estrogens	Anastrozole (Arimidex®) Letrozole (Femara®) Exemestane (Aromasin®)
Luteinizing hormone-releasing hormone (LHRH) agonists stops ovarian estrogen production	Leuprolide (Lupron®) Goserelin (Zoladex ®)

Hormone Therapy in Breast Cancer

For localized disease

Complete primary therapy (surgery, RT, chemotherapy)→ then start antiestrogen,

- If taking anti Her2 therapy, start with the maintenance anti Her-2 therapy

PreMenopausal → Tamoxifen for 5yr

- IF remains premenopausal
  - Take tamoxifen for another 5 yrs (10 yrs total) **OR**
  - Switch to an AI + ovarian suppression x5 yrs
- If becomes post menopausal
  - Take tamoxifen for another 5 yrs (10 yrs total) **OR**
  - Switch to an AI x5 yrs

*AI must be taken with ovarian suppression…(LHRH agonists)

Post Menopausal

- Tamoxifen for 5 to 10 years
- An AI for 5 to 10 years
- Tamoxifen x5 years, followed by AI for up to 5 years→ total 10 years of hormonal tx
- Tamoxifen for 2 to 3 years, followed by 2 to 8 years of an AI for a total of 5 to 10 years of hormonal tx

Hormone Therapy in Breast Cancer

For metastatic disease **AI preferred over Tamoxifen**

- May start with hormone therapy alone, prefer a 2 drug approach AI + CDK4/6 inhibitor
- If very symptomatic and/or visceral disease, may start with chemo x4-6 course and then hormone therapy

- AI + CDK 4/6 inhibitor (if premenopausal must add the LHRH angonist)
- Fulvestratran + CDK 4/6 inhibitor (if premenopausal must add the LHRH agonist)

Cyclin-dependent kinases (CDKs)

- Protein kinases that are “gatekeepers” to control transition through cell cycle
  - Transition between G1 and S is key checkpoint regulated by CDK 4/6 to protect against abnormal DNA replication
- CDK4 and CDK6 regulate proliferation in some epithelial cells, including ER-positive breast cancers, in which estrogen induces CDK4 and CDK6 activation
- Aromatase inhibitors and antiestrogens have been shown to suppress CDK4/6
- Reactivation of these kinases is one proposed mechanism of endocrine resistance
- CDK4/6 inhibitors, abemaciclib, palbociclib, and ribociclib are FDA approved for the treatment of ER-positive metastatic breast cancer in combination with antiestrogen therapies
- Inhibition of CDK4/6 blocks cell progression from G1 to S, causing cell cycle arrest
- No biomarkers have been identified to predict benefit from CDK inhibitors

Cyclin-dependent kinases (CDKs)

- No differences in efficacy, but some differences in S/E profile
- Myelosuppression, liver toxicity, diarrhea, rhythm disturbances

- Palbociclib and Ribociclib are associated with higher rates of neutropenia than abemaciclib
- Abemaciclib more frequently causes diarrhea
- Ribociclib has a highest incidence of liver function test abnormalities than other agents and can cause QTc prolongation, $\rightarrow$ may be less preferred for some patients (eg, those on QTc-prolonging agents)
- Abemaciclib is preferred CDK inhibitor in setting of brain metastases

Side Effects with Anti Estrogen Therapy in Breast Cancer

Menopause Related Symptoms

- Hot flashes/night sweats
- Vaginal dryness
- Urinary complaints
- Sexual dysfunction (dyspareunia)
- Sleep disturbance, mood disturbance, depression
- Cognitive
- Arthralgias/myalgias
- Fatigue

Menopause Related Health Risks

- Osteoporosis/bone fractures
- Cardiovascular disease

Thank you!

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