Hormones & Hormone Antagonists
Chapter 40 - Katzung

- Least toxic of anticancer drugs
- Highly selective
- Breast, endometrial, prostate cancers

5 Categories
- Androgens – Progestins
- Antiandrogens
- Gonadotropin-releasing hormone analogs
- Estrogens – Antiestrogens
- Aromatase inhibitors
Hormone Synthesis

**Progesterone**

$17\alpha$-Hydroxyprogesterone $\xrightarrow{\text{Aromatase}}$ Androstenedione $\xrightarrow{\text{Aromatase}}$ Testosterone

$\xrightarrow{\text{Aromatase}}$ Estrone $\xrightarrow{\text{Aromatase}}$ Estradiol
Androgens – *Breast cancer*

**Indications:** palliative therapy in advanced disseminated breast cancer

**MOA:** irreversible inhibitor of the enzyme steroid aromatase that is responsible for the synthesis of estrone from androstenedione

Hepatic metabolism, contraindicated in male breast cancer

- Most commonly used androgen for breast cancer.
- Few or no androgenic side effects - hirsutism
- Adrenal estrogen depletion – post menopausal women
Progestins - *endometrium*

**Indications:** palliative treatment of carcinoma of the breast or *endometrium*; off-label use: appetite stimulant in HIV

Not recommended during the first 4 months of pregnancy, must use at least 2 months of therapy to determine efficacy

**MOA:** Anti-leutinizing effect mediated by the pituitary gland and marked changes in progestational agent movement into the endometrium

Marked weight gain, thromboembolisms, USE contraception

**Indications:** *adjunctive and palliative treatment of inoperable metastatic recurrent endometrial cancer*, advanced breast cancer and renal carcinoma, Other – long acting contraceptive via IM injection

**MOA:** inhibits secretion of pituitary gonadotropin which prevents follicular maturation and ovulation, converts proliferative endometrium into secretory endometrium

May cause hepatic failure, avoid use in first 4 months of pregnancy, thromboembolism
Anti-Androgens - *prostate*

**Flutamide - Eulexin®**

Indications: metastatic carcinoma of the prostate

MOA: **non-steroidal anti-androgen** inhibits cellular uptake of androgen steroids and inhibits nuclear binding of androgens to their receptors - *adrenal*

Used with LHRH (GnRH) agonists, photosensitivity, inform patients of urine color changes, hepatic metabolism with renal excretion, 96% protein bound

**Nilutamide - Nilandron®**

Indications: For use in combo treatment with surgical castration for metastatic carcinoma of the prostate

MOA: **non-steroidal anti-androgen** that inhibits cellular uptake of testosterone and inhibits nuclear binding to its receptor - *adrenal*

Hepatic metabolism of methyl group produces two enantiomers in which one is major pcol active compound

Inhibits a variety of CYP enzymes, inform patients of night adaptation problems
Indications: Advanced prostate cancer

MOA: a non-steroidal competitive inhibitor of the cytosolic androgen receptors - adrenal

Prostatic carcinoma is androgen sensitive

Mixture of enantiomers - stereospecific metabolism occurs; R-enantiomer of the drug is predominate serum drug

Drug must be taken in combination with luteinizing-hormone releasing hormone (LHRH)
GnRH Agonists - prostate

- Gonadotropin-releasing hormone (GnRH)
- GnRH released from the hypothalamus
- Signals pituitary gland
- Agonists
  - Suppress testicular androgen production
  - Negative feedback inhibitor
  - Chemical Castration!
GnRH Agonists cont...

- **Leuprolide (Lupron)**
  - Synthetic analog of GnRH
  - Decreased androgen production in testes
  - SC or IM (q month, q 3 months)
    - Titanium implant (Viadur™; Duros®)
    - Polymeric dosing (Eligard™) every 3 months
  - Palliative: Advanced prostate carcinoma
  - **Doesn’t decrease adrenal androgens**
    - Add Flutamide!
  - Loss of libido, impotence

- **Gosarelin (Zoladex)**
  - SC pellet → upper abdomen
Indications: inoperable prostate cancer

Absolute contraindication in women

MOA: Non-steroidal estrogen that binds to cytosolic estrogen receptor with the complex being transported to the nucleus where androgenic activity is antagonized by receptor competition.

Primary hepatic metabolism with conjugated renally excreted.

Contraindicated in men with cancer of the breast, any estrogen dependent neoplasm, thromboembolic disorders.

Previously discussed prostatic carcinoma prodrug containing a mustard alkylating groups.

Diethylstibesterol diphosphate - Stilphostrol®

Estermustine Sodium Phosphate Emcyt® - Pharmacia & Upjohn
Antiestrogens

- Block estrogen receptors
- **Breast cancer ONLY!**
- All estrogen agonist/antagonists
- *Selective Estrogen Receptor Modulators*
  - *SERM’s*
Antiestrogens cont...

- **Tamoxifen (Nolvadex)**
  - Most widely Rx for breast cancer (DOC)!
  - P.O.
  - Used to:
    - Treat existing disease
    - Prophylaxis (high risk)
    - Post-surgery adjunct therapy
  - Estrogen stimulates tumor growth
  - Blocks tumor estrogen receptors

* Tumor must be receptor +
Tamoxifen cont...

- Receptor deactivation can:
  - Increase bone density
  - Reduce LDL levels – bad lipids
  - Increase HDL levels – good lipids
  - Increase cancer risk
    - Endometrial carcinoma
    - Thromboembolism
- Typical dose = 20 mg p.o. q.d.
Antiestrogens

Indications: Adjunctive treatment of breast cancer, prevention of breast cancer in genetically predisposed women and men

MOA: non-steroidal anti-estrogen that competes with estradiol for estrogen receptors in target breast tissues

Hepatic metabolism to conjugates that are renally excreted, hepatic failure possible, thromboembolism especially PE’s, have regular gynecologic exams, use only non-hormonal contraceptive methods

Indications: Breast cancer (ER + or unknown)

MOA: same as above

Extensively metabolized by CYP3A4, extensive enterohepatic recirculation

Watch for thromboembolism, leukopenia, may cause endometrial hyperplasia, patients with metastatic bone lesions may suffer hypercalcemia, if vaginal bleeding occurs immediately contact MD
Indications: Adjunctive treatment of breast cancer – Approved: April 2002

Intramuscular injection only given once monthly – 250 mg

MOA: Steroidal estrogen antagonist that competes with estradiol for estrogen receptors in target breast cancer tissues – down regulates the estrogen receptor protein present in human breast cancer cells - appears active against tamoxifen-resistant cell lines

No estrogen agonist activity

Highly protein bound to plasma protein including VLDL, LDL and HDL

Metabolism is primary CYP3A4 and some non-CYP450 processes with elimination 90% hepatobiliary

No known drug interactions to date other than possible CYP3A4 inducer effects
Aromatase Inhibitors

- Breast cancer drug class!!!
- Target: **post-menopausal women**
- Blocks estrogen production (androgens)
- Does NOT block ovarian production!
Aromatase Inhibitors

Progesterone

\[ 17\alpha\text{-Hydroxyprogesterone} \rightarrow \text{Androstenedione} \rightarrow \text{Estrone} \rightarrow \text{Estradiol} \]

\[ \text{Testosterone} \]
Aromatase Inhibitors

- **Anastrozole** (*Arimidex*)
  - *Gold Standard!*
  - Used when Tamoxifen fails
  - Not effective for ER- tumors!
  - As effective as Tamoxifen, fewer side-effects
  - *No apparent endometrial cancer risk!*

- **Letrozole** (*Femara*)

- **Exemestane** (*Aromasin*)
Aromatase Inhibitors

Letrozole - Femara®

Indications: Advanced breast cancer not responding to tamoxifen therapy; exemestane is also used to prevent prostate cancer, Anastrozole adjunct for breast cancer (new 2002)

MOA: inhibitors of the enzyme “aromatase” that is responsible for the conversion of adrenally produced androstenedione to estradiol - no effect on aldosterone synthesis

• Letrozole and Anastrozole are reversible competitive inhibitors
• Exemestrane is an irreversible inhibitor (suicide substrate)

Use caution in patients with hepatic and renal impairment

Anastrozole inhibits CYP 1A2, 2C8/9 and 3A4 at high dosages
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