### HORMONAL AGENTS USED IN CHEMOTHERAPY

- Estrogens
- Tamoxifen
- Aromatase inhibitors (anastrazole and exemestane)
- Estrogen receptor antagonists (fulvestrant)

### HORMONAL AGENTS USED IN CHEMOTHERAPY

- Gonadotropin-releasing hormone analogs (leuprolide)
- Androgens
- Antiandrogens (flutamide)
- Glucocorticoids (prednisone)

### TAMOXIFEN (Nolvadex)

### MECHANISM OF ACTION

- Competitive inhibition of estradiol binding to the estrogen receptor.
MECHANISM OF ACTION

• Competitive inhibition of estradiol binding to the estrogen receptor.

• Tamoxifen then inhibits expression of estrogen-regulated genes, including GF’s and angiogenic factors secreted by the tumor that may stimulate growth.

MECHANISM OF ACTION

• Induction of surrounding cells to produce the negative growth factor TGF-beta.

• Decreases local production of IGF-1 by surrounding tissues.

• Although inhibitory to tumors it has estrogen-like effects on bone and endometrial lining and increases the risk of thrombotic events.

PHARMACOKINETICS

• Readily absorbed when given orally.

• Metabolized to active metabolites.

• Long half life (given once daily).

TAMOXIFEN AND ITS MAJOR METABOLITES

ADVANCED BREAST CANCER

• Cytotoxic therapy and endocrine therapy are used.

• In HR-positive patients those treated with endocrine therapy have comparable response rates and longer times to progression, duration of response and survival vs chemotherapy.

ADVANCED BREAST CANCER

• Premenopausal women- ovarian removal or LH-RH agonist + tamoxifen

• Postmenopausal women-tamoxifen, aromatase inhibitors, ER antagonists.
THERAPEUTIC USES

• Palliative treatment for those with advanced breast cancer.

• Adjuvant therapy for breast cancer in pre- and post-menopausal patients.

• Chemo preventative agent for breast cancer.

TOXICITY

• Vasomotor symptoms (hot flashes).

• Atrophy of the lining of the vagina.

• Hair loss, nausea and vomiting.

• Menstrual irregularities, vaginal bleeding and discharge

TOXICITY

• Increased risk of thromboembolic events.

• Gynecologic complications.
  – endometrial cancer,
  – endometrial hyperplasia and
  – polyps and ovarian cysts)

TOXICITY

• Retinal deposits, decreased visual acuity and cataracts

• Liver enzyme changes

• Hypercalcemia

AROMATASE INHIBITORS

• Imidazole inhibitors – Anastrozole (Arimidex), Letrozole (Femara)

• Steroidal analogs – Exemestane (Aromasin)

MECHANISM OF ACTION

• After menopause the major biosynthetic pathway for estrogen production involves the conversion of androgens to estrogens in peripheral tissues.

• This is catalyzed by the aromatase enzyme.
MECHANISM OF ACTION

• Aromatase inhibitors inhibit conversion of adrenally-generated androstenedione to estrone by aromatase in peripheral tissues.

INHIBITION OF ESTROGEN BIOSYNTHESIS

THERAPEUTIC USES

• Metastatic breast cancer in postmenopausal women with receptor positive advanced breast cancer, or with disease progression after tamoxifen therapy.

IMIDAZOLE INHIBITORS

• Dominant AIs in clinical use.
• Oral route of administration.
• Rapid onset of action.
• Greater effectiveness in lowering serum estrogen levels.
• Hepatic metabolism.
• Favorable toxicity profiles (no androgenic side effects).

STEROIDAL AI’S

• Exemestane the most potent.
• Exemestane can be given orally, formestane IM.
**TOXICITY**

- GI disturbances are common.
- Hot flashes, vaginal drying.
- Lack of or loss of strength, headache, back pain.
- Androgenic properties (exemestane)—weight gain, acne, hypertrichosis.

**FULVESTANT (Faslodex)**

- Estrogen receptor antagonist.
- Metastatic breast cancer (hormone receptor positive in postmenopausal women) (second or 3rd line).
- Nausea, asthenia, pain, hot flushes and headache.

**GONATROPIN-RELEASEING HORMONE ANALOGS**

- Leuprolide (Lupron)
- Goserelin (Zoladex)
- Buserelin (Suprefact)
- Triptorelin (Trelstar Depot)

**MECHANISM OF ACTION**

- Biphasic effects on the pituitary.
- Initially they stimulate secretion of both FSH and LH.
- With longer term administration receptors become desensitized or down regulated and there is inhibition of the secretion of LH and FSH.

**MECHANISM OF ACTION**

- Concentration of testosterone falls to castration levels in men.
- Concentration of estrogens fall to postmenopausal values in women.

**PHARMACOKINETICS**

- Given parenterally in sustained release preparations.
THERAPEUTIC USES

• Prostate cancer (less toxic than DES and not irreversible like orchiectomy).
• Premenopausal breast carcinoma.

TOXICITY

• Transient flare of the disease.
• Hot flashes, gynecomastia, impotence, sweating, nausea, fatigue and decreases in bone and muscle mass.

PREDNISONE

• ALL
• CLL
• Lymphoma
• Hodgkin’s disease

ANTIANDROGENS

• Competitive inhibitors that prevent the natural ligands of the androgen receptor from binding.
• Steroidal and nonsteroidal agents.

STEROIDAL ANTIANDROGENS - CYPROTERONE

• Weak partial agonists and CI’s.
• Reduce LH and testosterone.
• Loss of libido, decreased sexual potency and low testosterone levels occur.
### FLUTAMIDE (Eulexin)
- Synthetic nonsteroidal antiandrogen.
- Inhibits ligand binding and translocation of androgen receptor from cytoplasm to nucleus.
- It does not inhibit LH or FSH production in the pituitary.
- Vasomotor flushing, gynecomastia etc occur but loss of sexual desire and potency are less.

### THERAPEUTIC USES
- Prostate cancer.
- Reduces the flare reaction induced by the testosterone surge during GnRH therapy.

### ADVERSE EFFECTS
- GI toxicity (diarrhea).
- Nausea, vomiting.
- Reversible liver toxicity—rare
- Gynecomastia and nipple tenderness, some loss of sexual function, decreased libido, hot flashes.

### DIFFERENTIATION INDUCING AGENTS
- Redirect cells toward their normal phenotype and therefore may reverse or suppress evolving malignant lesions.
- Retinoic acid derivatives
- Arsenic

### BEXAROTENE (Targretin)
- Selectively activates retinoid X receptors which when activated function as transcription factors that regulate expression of genes that control cellular differentiation and proliferation.

### THERAPEUTIC USES
- Used orally for the treatment of skin manifestations of cutaneous T cell lymphoma in patients refractory to at least one prior systemic therapy.
ADVERSE EFFECTS
• Most patients develop lipid abnormalities including hypertriglyceridemia, hypercholesterolemia and decreased HDL.
• Hypothyroidism occurs commonly.

TREATMENT USES
• Acute Promyelocytic Leukemia

TRETINOIN (Vesanoid) (ATRA, All trans retinoic acid)
• Binds retinoic acid receptors
• Induces differentiation

ADVERSE EFFECTS
• Dry skin, rash, pruritus
• Headache
• Arrhythmias
• Liver enzyme increases
• Retinoic acid syndrome

RETINOIDS
• Alitretinoin (Panretin) for the topical treatment of cutaneous lesions in patients with AIDS-related Kaposi’s sarcoma.
13-CIS-RETINOIC ACID (Isotretinoin)

- Chemopreventative adjuvant to prevent second primary tumors in patients with head and neck squamous cell carcinoma.

ARSENIC TRIOXIDE (Trisenox)

THERAPEUTIC USES

- Refractory or relapsed acute promyelocytic leukemia.

TOXICITY

- APL differentiation syndrome.
- Increases in the QT interval.
- Hyperleukocytosis.
- GI complaints.

MOLECULAR TARGETED THERAPY

- Identify molecular target in tumor cells.
- Develop drugs to target only tumor cells.
MOLECULARLY TARGETED THERAPY

- Monoclonal antibodies
- Signal transduction inhibitors
- Antisense therapy

MONOCLONAL ANTIBODIES

- Long considered potential anti-cancer agents because of their specificity for cell-membrane antigens.
- Hybridoma and recombinant technology have led to the production of unlimited quantities of clinical grade murine, chimeric, and humanized monoclonals.

MECHANISM OF ACTION

- Bind to cell surface antigens.
- Antibody-dependent cell-mediated cytotoxicity (ADCC).
- Complement-mediated cytotoxicity.

MECHANISM OF ACTION

- They may directly cause growth inhibition, cell cycle alteration, and apoptosis.
- Sensitization to the effects of conventional cytotoxic agents (additive and synergistic effects).

MONOCLONAL ANTIBODIES

- Monoclonal Antibodies (Rituximab, Trasztuzumab, Bevacizumab).
- Monoclonal Antibody-Drug Conjugates (Gemtuzumab).
- Monoclonal Antibody-Toxin Conjugates.
- Monoclonal Antibody-Radionuclide Conjugates ($^{131}$I-Tositumomab).

RITUXIMAB (Rituxan)

- It is a chimeric mouse/human anti-CD20 antibody.
- Binds to the CD20 antigen found on the surface of most normal and malignant B cells.
RITUXIMAB (Rituxan)

• A genetically engineered monoclonal antibody for the treatment of non-Hodgkin’s lymphoma.

• It is a chimeric mouse/human anti-CD20 antibody.

• Binds to the CD20 antigen found on the surface of most normal and malignant B cells.

MECHANISM OF ACTION

• Depletes B cells but does not affect stem cells.

• Sensitizes lymphoma cells to the cytotoxic effects of some anticancer drugs.

MECHANISM OF ACTION

• It mediates complement-dependent cell lysis and antibody-dependent cellular cytotoxicity in chemoresistant human lymphoma cells and induces apoptosis.

• Depletes B cells but does not affect stem cells.

• Sensitizes lymphoma cells to the cytotoxic effects of some anticancer drugs.

THERAPEUTIC USES

• Non-Hodgkin’s Lymphomas

• CLL

ADVERSE EFFECTS

• Infusion related symptoms such as fever and chills with the first dose.

• Bone marrow suppression.

• Tumor lysis syndrome

• Severe mucocutaneous reactions.

TRASTUZUMAB (Herceptin)

• A recombinant humanized monoclonal antibody that binds to a protein encoded by the oncogene HER2/neu (Erb-2).

• Member of the EGF family of receptors. Encodes a tyrosine kinase.
THERAPEUTIC USES

- Breast cancer (alone in patients refractory to chemotherapy or with paclitaxel).

TOXICITY

- Infusion related events (pain, asthenia, chills etc.).
- Allergic reactions.
- Cardiotoxicity (ventricular dysfunction and congestive heart failure).

CETUXIMAB (Erbitux)

- Binds to the human EGFR
- Colon cancer

BEVACIZUMAB (Avastin)

- Recombinant human/mouse antibody that binds to VEGF.
- Colon cancer

EDRECOLOMAB

- Used in treatment of colorectal cancer.
ALEMTUZUMAB (Campath)

- Humanized monoclonal that targets CD52, an antigen present on the surface of essentially all B and T lymphocytes.
- After binding to the cell-surface antigen, it is believed to be involved in a sequence of events leading to leukemic cell lysis.

THERAPEUTIC USES

- Patients with CLL who have not responded to therapy with alkylating agents and fludarabine.
- Low grade lymphomas.

MONOCLONAL ANTIBODY CONJUGATES

- Antibodies may serve as the guiding or targeting system for other cytotoxic pharmaceutical products such as radiolabelled cpds., toxins, and antibiotics.

GEMTUZUMAB (Mylotarg)

- Antibody-cytotoxic antibiotic conjugate.
- Gemtuzumab is a recombinant humanized antibody that binds to CD33-positive AML.
- The complex is taken up into the cell where the antibiotic calicheamicin is released causing double strand breaks in the DNA and cell death.

GEMTUZUMAB

- AML (in older patients who are in first relapse and are not candidates for cytotoxic chemotherapy).

TOXICITY

- Infusion-related reactions.
- Neutropenia.
MONOCLONAL ANTIBODY-RADIONUCLEOTIDE CONJUGATES

- IODINE-131 TOSITUMONAB (Bextar)
- Yttrium-90 IBRITUMOMAB TIUXETAN (Zevulin)

MECHANISM OF ACTION

- Radiolabeled antibodies.
- React with the CD20 molecule.
- Targets radiation to the B cells it binds to, and to neighboring cells.

THERAPEUTIC USES

- Treatment of patients with relapsed or refractory low grade non-Hodgkins lymphoma.

ANTIANGIOGENIC THERAPY

- Synthetic/semi-synthetic inhibitors (marimastat, thalidomide).
- Endogenous inhibitors (angiostatin and endostatin).
- Biological antagonists (VEGF inhibitors and receptor blockers).
- Vascular targeting (Antibody targeting, vascular gene therapy).

ANTI-INVASION AND ANTI-METASTASIS THERAPY

- Prevention of invasion and metastasis is perhaps the most important issue in cancer treatment.
- With a clearer understanding of the biology of invasion and metastasis more strategies have been explored in order to limit metastatic spread.

ANTI-INVASION AND ANTI-METASTASIS THERAPY

- No successful clinical application has yet come but many agents/approaches have shown promise.
- Inhibition of ECM degradation.
- Inhibition of angiogenesis.
ANTI-INVASION AND ANTI-METASTASIS THERAPY

- Anti-motility agents.
- Promotion of cell-cell adhesion.
- Cytokines and anti-cytokines.
- Gamma linolenic acid and polyunsaturated fatty acids.
- Anti-signalling.

INHIBITORS OF EXTRACELLULAR MATRIX DEGRADATION

- MMP inhibitors
- Antisense Oligonucleotides
- Antibodies to proteolytic enzymes.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

- Tyrosine kinase pathways
- Ubiquitin pathway
- Ras Signaling

IMATINIB (Gleevec, STI-571)

- Inhibits the BCR-ABL tyrosine kinase created by the Philadelphia chromosome in CML.
RESISTANCE

PHARMACOKINETICS

• Well absorbed after oral administration.
• Metabolized in the liver.

THERAPEUTIC USES

TOXICITY

• CML
• GI stromal tumors (GISTs)
• Ph⁺ ALL
• Thrombocytopenia and neutropenia.
• Nausea and vomiting and diarrhea
• Severe fluid retention
• Muscle cramps
• Rash
• Hepatotoxicity

GEFITINIB (Iressa)

• An inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase.
• Most non small cell lung cancers express high quantities of EGFR.
• Gefitinib is a highly selective inhibitor.

THERAPEUTIC USES

• Non-small lung cancer in patients who have failed standard chemotherapy.
<table>
<thead>
<tr>
<th><strong>TOXICITY</strong></th>
<th><strong>ERLOTINIB (Tarceva)</strong></th>
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<tbody>
<tr>
<td>• Pulmonary toxicity.</td>
<td>• Selective EGFR TK inhibitor</td>
</tr>
<tr>
<td>• Liver toxicity.</td>
<td>• Non small cell lung cancer.</td>
</tr>
<tr>
<td>• Dose-related diarrhea and an acne-like rash have occurred commonly.</td>
<td>• Diarrhea and rash are the most common adverse effects.</td>
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<tr>
<td>• Myelosuppression has not occurred.</td>
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<tr>
<th><strong>BORTEZOMIB (Velcade)</strong></th>
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<tr>
<td>• Boronic acid analog that is a reversible inhibitor of the 26s proteasome, which degrades proteins involved in signal transduction.</td>
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<tr>
<td>• Refractory multiple myeloma.</td>
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