Cancer Pharmacotherapy

http://www.pharmacology2000.com/index.htm

Dorothee von Laer

FIRST Catch-up Course: CuC1

Basics in Medicine and Pharmacology for Scientists

- Cancer = malignancy =malignant neoplasm/tumor
  - Proliferation
  - Dedifferentiation
  - Invasion
  - Metastasis

Role of Chemotherapy in Cancer Treatment

- **(1) Metastatic cancer:**
  - **Palliative or**
  - **curative chemotherapy**
- **(2) Adjuvant chemotherapy:**
  - **to erradicate or control micro-metastasis**
- **(3) Neo-adjuvant chemotherapy (Induction chemotherapy)**
  - **to make surgery of tumor possible**
  - **to alleviate surgical damage**
  - **to eradicate micro-metastasis**
- **(4) Hematological Malignancies:**
  - **primary treatment**

Cytotoxic anticancer drugs

- Kills fixed percentage of cells, so complete elimination difficult
- Act on dividing cells (S, G2 or M)
- Unspecific mode of action thus
- Severe side effects

Chemotherapy Curable Cancers

- **Childhood:**
- ALL 70%
- NHL >50%
- **Burkitt's Lymphoma** >50%
- Wilm's Tumor >50%
- Ewing's Sarcoma >50%
- Embryonal Rhabdomyosarcoma >50%

- **Adult:**
- Chorio-Carcinoma 90%
- Testis Cancer >75%
- Hodgkins' Disease 70%
- Aggressive NHL >50%
- AML 25%-50%
- Ovarians Cancer 10%-20%

Chemo-Resistant (Insensitive) Cancers

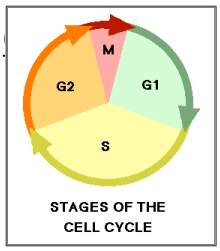
Non-Small Cell Lung Cancer
G.I. Cancers
Pancreatic Cancer
Melanoma

Common unwanted Side Effects of Cytotoxic Cancer Drugs

- Myelosuppression (Bone marrow toxicity)
- Impaired wound healing
- Loss of hair
- Damage of gastrointestinal epithelium
- Depression of growth in children
- Sterility
- Teratogenicity
- Carcinogenicity
- Nausea, vomiting

Classes Anticancer Drugs

- Cytotoxic
  - Alkylating agents
  - Antimetabolites
  - Cytotoxic antibiotics
  - Plant derivatives
- Hormones
- Miscellaneous Agents



STAGES OF THE CELL CYCLE

Cell Cycle Specific Agents

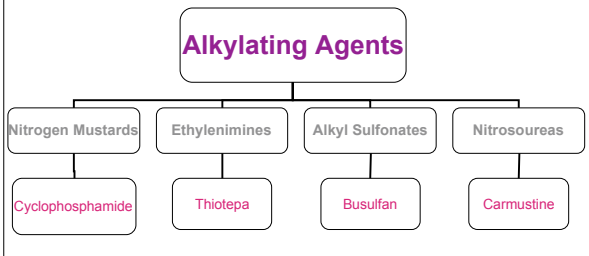
- Antimetabolites
- Bleomycin
- Podophyllin Alkaloids
- Plant Alkaloids

Cell Cycle Non-Specific Agents

- Alkylating Agents
- Antibiotics
- Cisplatin
- Nitrosoureas

Cytotoxic drugs: Alkylating agents

- Not cell cycle specific
- Alkylate within DNA at the N7 position of guanine
- Results in miscoding through abnormal base-pairing with thymine or in depurination by excision of guanine residues, leading to strand breakage
- Cross-linking of DNA and ring cleavage
  - ✓ Nitrogen Mustards: cyclophosphamide, melphalane, chlorambucil
  - ✓Nitrosureas: lomustin carmustin
  - ✓Busulfane
  - ✓Cisplatin
  - ✓Carboplatin



Alkylating Agents
Mechanism of Action

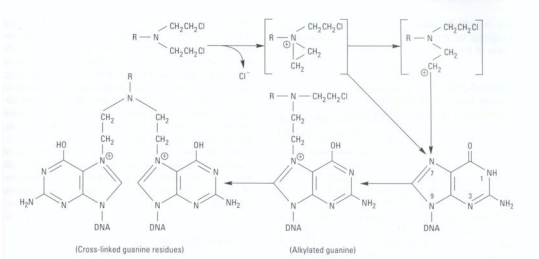


Figure 55–5. Mechanism of alkylation of DNA guanine. A bis(chloroethyl)amine forms an ethyleneimonium ion and a carbonium ion that react with a base such as N7 of guanine in DNA, producing an alkylated purine. Alkylation of a second guanine residue, through the illustrated mechanism, results in cross-linking of DNA strands.

Cyclophosphamide

- Most common alkylating agent
- Acts on lymphocytes
- Can be used as immunosuppressant
- Activated by P450 mixed function oxidases
- Specific USE: cystitis by acrolein (inactivated by Mesna)

Cyclophosphamide Metabolism

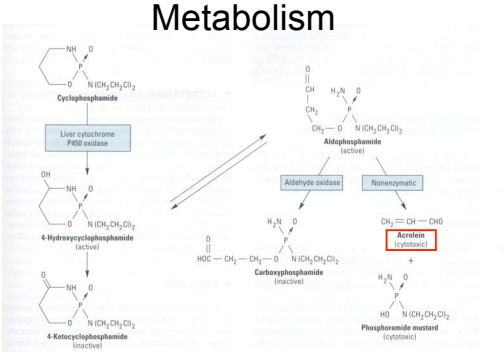


Figure 55–6. Cyclophosphamide metabolism.

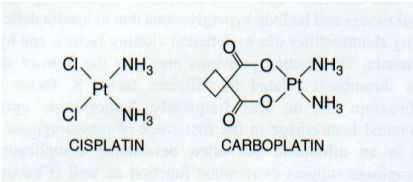
Other alkylating agents

Nitrosureas: lomustine, carmustine, cross BBB

Busulphane: Selective on bone marrow

Cisplatin: highly toxic, severe nausea, nephrotoxic

Platinum Coordination Complexes



These compounds alkylate N7 of guanine. They cause nephro- and ototoxicity. To counteract the effects of nephrotoxicity, give mannitol as an osmotic diuretic, or induce chloride diuresis with 0.1% NaCl.

Alkylating Agents Toxicity

- Bone marrow depression, with leukopenia and thrombocytopenia

- *Cyclophosphamide/Ifosfamide* - hemorrhagic cystitis
  - Reduced by coadministration with MESNA
- *Cisplatin/Carboplatin* - ototoxic and nephrotoxic
  - Nephrotoxicity reduced by chloride diuresis and hydration

Alkylating Agents Therapeutic Uses

Used to treat a wide variety of hematologic and solid tumors

- *Thiotepa* – ovarian cancer
- *Busulfan* – chronic myeloid leukemia
- *Nitrosoureas* - brain tumors
- *Streptozocin* – insulin-secreting islet cell carcinoma of the pancreas

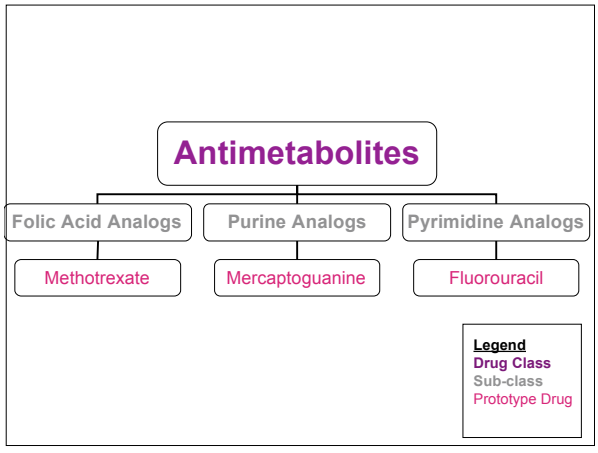
Antimetabolites

Block of subvert pathways in DNA synthesis

•Folate antagonists: Methotrexate
~Inhibits dihydrofolate reductase
~Folates essential for purine and thymidylate synthesis
~Specific USE: Nephrotoxicity, Pneumonitis

•Pyrimidine Analogues
~Fluorouracil, Cytarabine

•Purine Analogues
~Fludarabine, pentostatin, cladribine, mercaptopurine, thioguanine



Folate

- An essential dietary factor, from which THF cofactors are formed which provide single carbon groups for the synthesis of precursors of DNA and RNA
- To function as a cofactor folate must be reduced by DHFR to THF

Methotrexate
Mechanism of Action

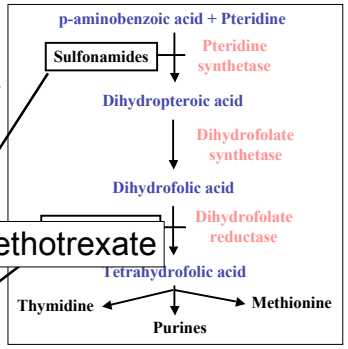
- The enzyme DHFR is the 1º site of action
- MTX prevents the formation of THF, causing an intracellular deficiency of folate coenzymes and accumulation of the toxic inhibitory substrate, DHF polyglutamate
- The one carbon transfer reactions for purine and thymidylate synthesis cease, interrupting DNA and RNA synthesis

Inhibitors of Folic Acid Synthesis

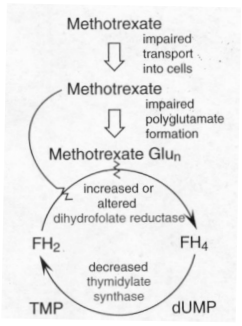
- Basis of Selectivity: eukaryotes have transporter for folic acid.
- Folic Acid Metabolism

Compete with PABA

Enzyme inhibitor



Resistance



Methotrexate
Therapeutic Uses

- psoriasis, rheumatoid arthritis,
- acute lymphoblastic leukemia, meningeal leukemia,
- choriocarcinoma, osteosarcoma,
- mycosis fungoides, Burkitt's and non-Hodgkin's lymphomas,
- cancers of the breast, head and neck, ovary, and bladder

Therapeutic Uses of 5-FU

- Metastatic carcinomas of the breast and the GI tract
- hepatoma
- carcinomas of the ovary, cervix, urinary bladder, prostate, pancreas, and oropharyngeal areas
- Combined with levamisole for colon cancer

Cytotoxic Antibiotics

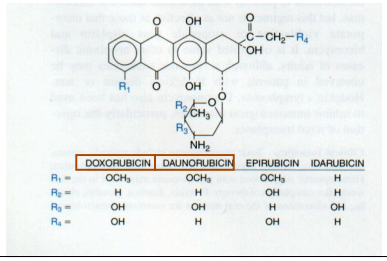
•Mostly direct action on DNA
•Anthracyclins:
  - ➢Doxyrubicine, idarubicine, aclarubicine, mitozantrone
  - ➢Doxirubicine binds to DNA
  - ➢Blocks topoisomerase II (DNA gyrase)
  - ➢Specific USE: cardiotoxicity

•Dactinomycin:
  - ➢binds minor groove, inhibits transcription

•Bleomycins:
  - ➢Glycopeptide
  - ➢Cause DNA chain fragmentation
  - ➢Specific USE: pulmonary fibrosis, allergic reactions

Anthracyclines

- Doxorubicin
- Daunorubicin

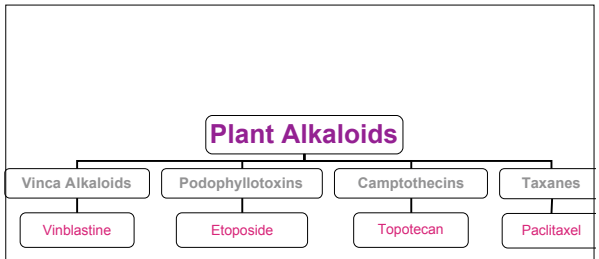


Plant Derivatives

- Vinca alkaloids (periwinkle plant, Immergrün):
  - Vincristine, vinblastin + vindesine
  - Bind tubulin, inhibit its polymerisation and spindle formation
  - Act on metaphase
  - Relatively untoxic
  - Specific USE: neuromuscular
- Taxanes (Yew = Eibe)
  - Paclitaxel, Docelatel
  - Freezes microtubules
  - Breast + ovarian cancer
  - Specific USE: Hypersensitivity, neurotoxicity
- Podophyllotoxinds (mayapple root):
  - Etoposide
  - Blocks topoisomerase II

Mayapple Fußblatt
Comon Periwinkle plant

Vinca Alkaloids

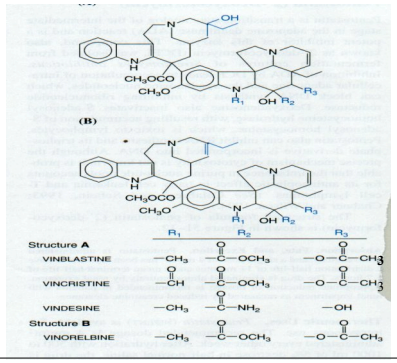


Vinca Alkaloids
Mechanism of Action

- Bind to the microtubular protein tubulin in a dimeric form
- The drug-tubulin complex adds to the forming end of the microtubules to terminate assembly
- Depolymerization of the microtubules occurs
- Resulting in mitotic arrest at metaphase, dissolution of the mitotic spindle, and interference with chromosome segregation
- CCS agents- M phase

Vinca Alkaloids

Inhibit microtubules (spindle), causing metaphase cell arrest in M phase.



Resistance mechanisms to cytotoxic anticancer drugs

- Increased export of the drug. Efflux-pump mdr-1 (P-glycoprotein) especially for natural compounds
- Reduced uptake
- Reduced activation of drug, e.g. purin-/ pyrimidine antagonists
- Increased inactivation
- Increased concentration of target enzyme (methotrexate)
- Decreased requirement for substrate (crisantaspase)
- Alternative pathways (anti-metabolites)
- Repair (alkylating agents, MGMT)
- Altered activity of target (eg topoisomerase II, doxorubicin)
- Suppression of apoptosis by upregulation of bcl-2 + p53 mutations

Schematic of P-glycoprotein

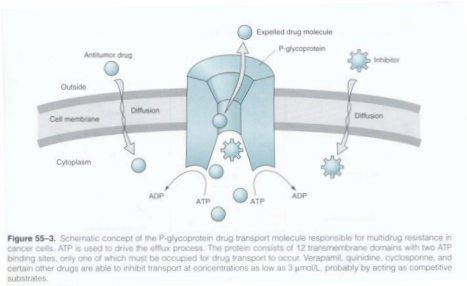


Figure 55–3. Schematic concept of the P-glycoprotein drug transport molecule responsible for multidrug resistance in cancer cells. ATP is used to drive the efflux process. The protein consists of 12 transmembrane domains with two ATP binding sites, only one of which must be occupied for drug transport to occur. Verapamil, quinidine, cyclosporine, and certain other drugs are able to inhibit transport at concentrations as low as 3 μmol/L, probably by acting as competitive substrates.

Miscellaneous Anti-Cancer Agents

- Asparaginase
- Hydroxurea
- Mitoxantrone
- Mitotane
- Retinoic Acid Derivatives
- Amifostine

Asparaginase

- An enzyme isolated from bacteria
- Causes catabolic depletion of serum asparagine to aspartic acid and ammonia
- Resulting in reduced blood glutamine levels and inhibition of protein synthesis
- Neoplastic cells require external source of asparagine
- Treats childhood acute leukemia
- Can cause anaphylactic shock

Hydroxyurea

- An analog of urea
- Inhibits the enzyme ribonucleotide reductase
- Resulting in the depletion of deoxynucleoside triphosphate pools
- Thereby inhibiting DNA synthesis
- S-phase specific agent
- Treats melanoma and chronic myelogenous leukemia

Mitoxantrone

- Structure resembles the anthracyclines
- Binds to DNA to produce strand breakage
- Inhibits DNA and RNA synthesis
- Treats pediatric and adult acute myelogenous leukemia, non-Hodgkin's lymphomas, and breast cancer
- Causes cardiac toxicity

Mechanisms & Actions of Useful Chemotherapeutic Drugs in Neoplastic Disease

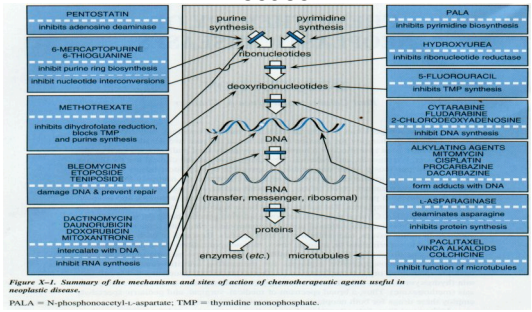
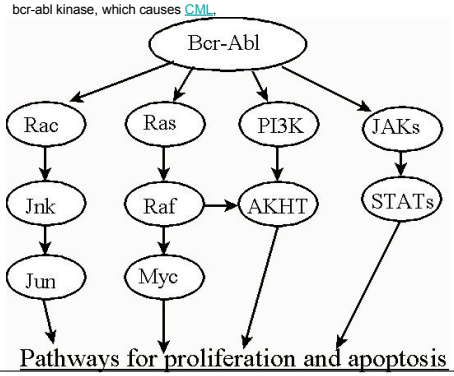


Figure X–1. Summary of the mechanisms and sites of action of chemotherapeutic agents useful in neoplastic disease.

PALA = N-phosphonoacetyl-L-aspartate; TMP = thymidine monophosphate.

Signal transduction

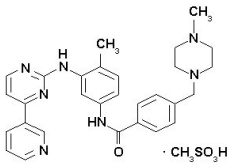
bcr-abl kinase, which causes CML,

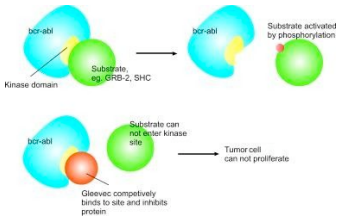


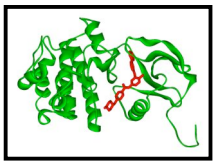
Signal transduction

•**Tyrosine Kinase Inhibitors**

Imatinib (Gleevec) is the first market drug that introduced for Chronic Myeloid Leukaemia (CML)

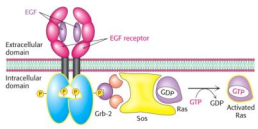






bcr-abl kinase, which causes CML, inhibited by imatinib (small molecule).

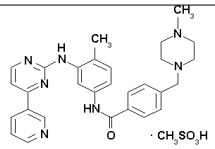
Signal transduction



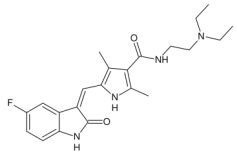
- **Sunitinib** (Sutent) is an orally-available small-molecule multiple receptor tyrosine kinase inhibitor.
  - Pfizer
    Approved January 2006
    Kidney Cancer/Gastrointestinal Stromal Tumors
- **Sorafenib** (Nexavar) is a multikinase inhibitor targeting a number of serine/threonine and receptor tyrosine kinases.
  - Bayer/Onyx
    Approved December 2005
    Renal Cell Carcinoma

http://www.centerwatch.com/patient/drugs/dru867.html

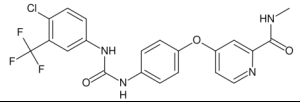
Imatinib (Gleevec by Novartis)



Sunitinib (Sutent by Pfizer)



Sorafenib (Nexavar by Bayer)



Inducers of apoptosis and/or differentiation

Clinical therapeutics targeting caspases

TABLE 2
New drugs and approaches targeting caspases

Reagent	Principle	Company/Reference	Experimental Effects	Clinical Trial/Status
IDN-6556	Peptidomimetic irreversible caspase inhibitor	Idun	Antiapoptotic, anti-inflammatory and antifibrotic in models of liver damage	Phase 2 started for chronic HCV infection, Phase 2 opened for HBV infection and ischemia/reperfusion injury of liver transplants
IDN-6734	Caspase inhibitor	Idun	Reduces heart muscle damage in animal models of heart attack	Phase 1, acute myocardial infarction
VX-799	Small molecule caspase inhibitor	Vertex/Serono	Effective in sepsis and neuronal cell death models	Phase 1, started in 2003 for septic organ failure
MX-1013	Dipeptide pan-caspase inhibitor	Maxim	Prevents apoptosis in animal models of myocardial infarct, stroke, and spinal cord injury	Preclinical, developed for myocardial infarct, stroke, acute liver failure
MX-2060 derivatives	Small molecule caspase activators	Maxim	Found in a cell-based caspase screen, growth inhibition in a rat tumor model	Preclinical
M-920	Broad spectrum caspase inhibitor	Merck Frosst	Effective against septic shock in a mouse model	Preclinical
Small molecule compounds	Caspase activators	Genzin X	Caspase activators in cancer but not normal cells	Preclinical
RGD peptides	Caspase activators	Merck Frosst, Maxim	Apoptosis induction in tumor cell lines	Preclinical
IDN-11104 VX-740 (Pralnacasan)	ICE inhibitor ICE inhibitor	Idun Vertex/ Aventis	Anti-inflammatory in rheumatoid and osteoarthritis models	Preclinical Phase 2, rheumatoid arthritis patients showed anti-inflammatory effects
VX-765 M-926	ICE inhibitor Reversible caspase-3 inhibitor	Vertex Merck Frosst	Anti-inflammatory in animal models Protects mice against neonatal hypoxia-ischemia, rescues neurons in a Huntington's disease model	Phase 2a planned for psoriasis Preclinical
M-791	Caspase-3 specific inhibitor	Merck Frosst	Effective against septic shock in a mouse model	Preclinical
Immunocasp-3, Immunocasp-6	Cell-permeable HER2 mAb fused to caspase-3 or -6	Jia et al., 2003; Xu et al., 2004	Growth inhibition of HER2-positive tumors in a mouse xenograft model	Preclinical
Ad-GSCasp3	Adenoviral chemically inducible caspase-3	Shariat et al., 2001	Reduction in tumor growth in a prostate cancer mouse model	Preclinical
FKF-F8-CP3	Caspase-3 fusion construct with a-mifepristone	Tse and Rabbitts, 2000	Antigen-dependent induction of apoptosis	Preclinical
FKBP12/casp-9 fusionprotein	Chemically inducible caspase-9	Nur et al., 2002	Antiangiogenic in mouse models upon induction of caspase-9 dimerization	Preclinical

Companies: Avantis (www.avantis.com), Genzin X Biotechnologies (www.genzinx.com), Idun Pharmaceuticals, Inc. (www.idun.com), Maxim Pharmaceuticals (www.maxim.com), Merck Frosst Canada & Co. (www.merckfrosst.ca), Sumao (www.sumao.com), Vertex Pharmaceuticals, Inc. (www.vpharm.com).

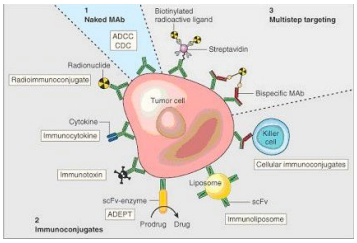
APOPTOSIS-BASED THERAPIES

Fischer et al, 2005

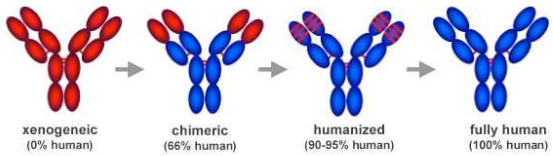
Biologics

- Crisantaspase: Asparaginase digests Asparagine, most cancer can't synthesize Asparagine (eg ALL)
- Mabs
- Biological response modifiers:
  - IL-2
  - Interferons

Antibodies: mode of action



Mab in therapy



Approved Mab for cancer

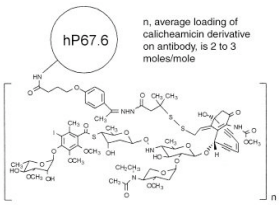
Monoclonal Antibodies Used to Treat Cancer

MAb Name	Trade Name	Used to Treat:	Approved in:
Rituximab	Rituxan	Non-Hodgkin lymphoma	1997
Trastuzumab	Herceptin	Breast cancer	1998
Gemtuzumab ozogamicin*	Mylotarg	Acute myelogenous leukemia (AML)	2000
Alemtuzumab	Campath	Chronic lymphocytic leukemia (CLL)	2001
Ibritumomab tiuxetan*	Zevalin	Non-Hodgkin lymphoma	2002
Tositumomab*	Bexxar	Non-Hodgkin lymphoma	2003
Cetuximab	Erbitux	Colorectal cancer Head & neck cancers	2004 2006
Bevacizumab	Avastin	Colorectal cancer Non-small cell lung cancer	2004 2006
Panitumumab	Vectibix	Colorectal cancer	2004

*conjugated monoclonal antibodies

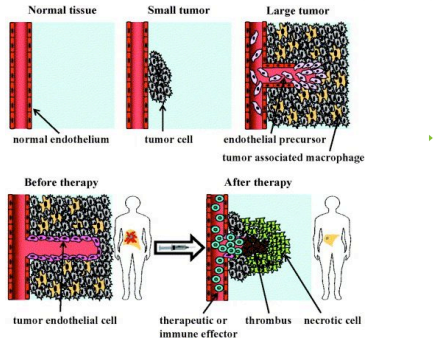
Rituximab (anti-CD20) and Alemtuzumab (anti-CD52) act through host immune system
Trastuzumab (anti-Her2/neu), Cetuximab and Panitumumab (both anti-EGFR) block receptor activity
Bevacizumab (anti-VEGF) is anti-angiogenic
Ibritumomab tiuxetan and Tositumomab are radiolabeled anti-CD20 mab

Gemtuzumab ozogamicin is calicheamicin attached to anti-CD33



Anti-Angiogenics

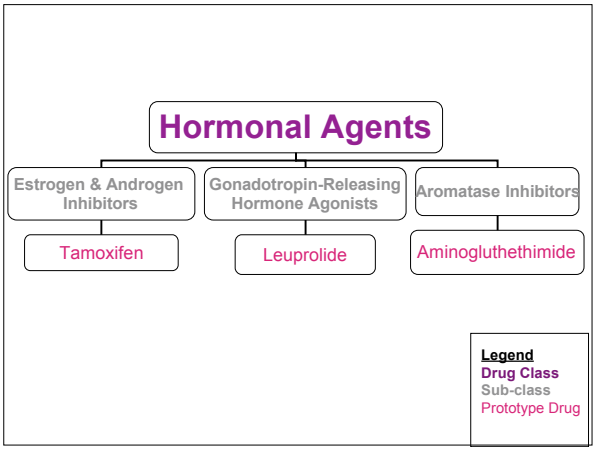
Bevacizumab (Avastin)



Vaccines targeting tumor angiogenesis—a novel strategy for cancer immunotherapy
Y. Okaji et al, 2006

Hormones

- Glucocorticoids -> Lymphatic leukemias + lymphomas
- Progesteron-> Endometrial cancer
- Gonadotrophin releasing hormone analogues: cyproterone, inhibits gonadotrophin release. -> prostate cancer
- Anti-estrogens/tamoxifen-> hormone-dependent breast cancer


Hormonal Agents
Estrogen & Androgen Inhibitors
Gonadotropin-Releasing Hormone Agonists
Aromatase Inhibitors
Tamoxifen
Leuprolide
Aminogluthethimide
Legend
Drug Class
Sub-class
Prototype Drug