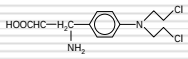
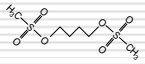
Classes of Antineoplastic Agents

ALKYLATING AGENTS

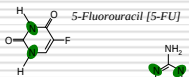


Melphalan [Nitrogen Mustard]

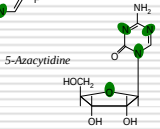


Busulfan [Alkyl sulfonate]

ANTIMETABOLITES

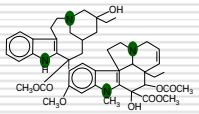


5-Fluorouracil [5-FU]



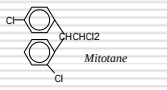
5-Azacytidine

NATURAL PRODUCTS

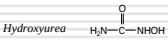


Vinblastine [V. rosea Alkaloid]

MISCELLANEOUS

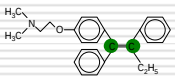


Mitotane



Hydroxyurea

HORMONES & ANTAGONISTS



Tamoxifen [Estrogen receptor antagonist]

EXPERIMENTAL & NEW AGENTS

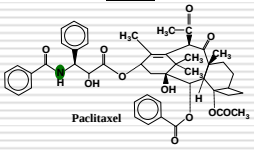
Trastuzumab [Anti-EGFR mAb]
Rituximab [Anti-CD20 mAb]

Natural Products

Class of natural product	Drugs in class	Disease
1. Vinca alkaloids	Vinblastine Vincristine Vinorelbine	Hod/Non-hod lym Mainly solid tumors
2. Taxanes	Paclitaxel [Taxol] Docetaxel	Solid
3. Epipodophyllotoxins	Etoposide Teniposide	Solid
4. Camptothecins	Topotecan Irinotecan	Solid
5. Antibiotics	Actinomycin D Daunorubicin Doxorubicin Bleomycin Mitomycin C	Solid
6. Enzymes	L-Asparaginase	Leu [ALL]

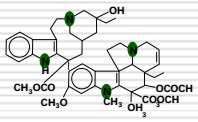
Natural Products

Taxanes



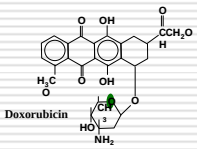
Paclitaxel

Vinca alkaloids



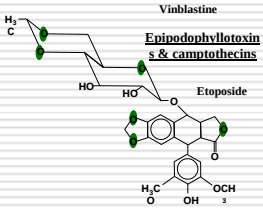
Vinblastine

Antibiotics



Doxorubicin

Epipodophyllotoxins & camptothecins

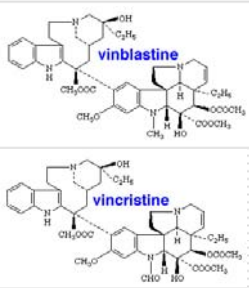


Etoposide

Vinca alkaloids

(Vinblastine, Vincristine)

- These drugs block the formation of mitotic spindle by **preventing the assembly** of tubulin dimers into microtubules
- They act primarily on the M phase of cancer cell cycle
- Resistance is due to increased efflux of drugs from tumor cells



Vinca alkaloids

(Vinblastine, Vincristine)

VinBlastine	**Vin**Cristine (oncovan)
Uses	Uses
Hodgkin's disease Lymphomas Carcinoma **B**reast Testicular tumors	**C**hildhood leukemias **C**hildhood tumors-Wilm's tumor, Neuroblastoma, Hodgkin's disease
Toxicity:	**Toxicity:**
Bone marrow suppression, anorexia, nausea, vomiting & Diarrhea, Alopecia	Peripheral neuritis with Paresthesia, Muscle weakness Vincristine has marrow sparing effect

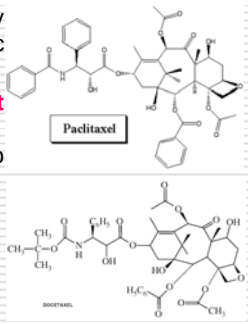
Taxanes:

Paclitaxel, Docetaxel

- These drugs act by interfering with mitotic spindle
- They **prevent micotubule disassembly** into tubulin monomers

Toxicity:

- Neutropenia
- Peripheral neuropathy



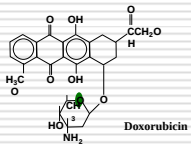
Anticancer Antibiotics

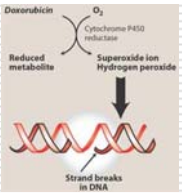
- Anthracyclines:
  - Doxorubicin (Adriamycin)
  - Daunorubicin
- Bleomysin
- Dactinomycin
- Mitomycin

Anticancer Antibiotics

Doxorubicin & Daunorubicin

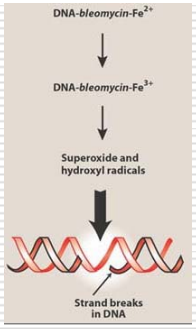
- These drugs intercalate between base pairs, inhibit topoisomerase II and also generate free radicals
- They block RNA and DNA synthesis and cause strand scission
- These are CCNS drugs
- Used as a component in ABVD regimen in Hodgkin's lymphoma





Anticancer Antibiotics

Bleomycin



- Acts through binding to DNA, which results in single and double strand breaks following free radical formation and inhibition of DNA synthesis
- The DNA fragmentation is due to *oxidation of a DNA-bleomycin-Fe(II) complex and leads to chromosomal aberrations*
- CCS drug that causes accumulation of cells in G_2

Uses

- ABVD regimen for Hodgkin's
- Intracavitary therapy in ovarian and breast cancers (Sclerosing agent)

Toxicity:

- Pulmonary fibrosis

Hormones

- Breast and Prostate cancers frequently demonstrate hormone-dependent growth (at least in early stage disease)
- Classes:
  - Glucocorticoids
  - Sex hormone antagonists
  - GnRH analogs
  - Aromatase inhibitors

Hormones

- Tumors derived from tissues responding to hormones may be hormone-dependent
  - Growth inhibited by hormone antagonists

    OR
  - Other hormones with opposing actions

    OR
  - Inhibitors of relevant hormone

Glucocorticoids (Prednisone)

- Inhibitory on lymphocyte proliferation
- Used against leukemias, lymphomas
  - Have anti-inflammatory effect
  - Increase appetite
  - Produce euphoria (feeling of well being)
  - Increase body weight
  - Suppress hypersensitivity reaction due to certain anticancer drugs
  - Control hypercalcemia
  - Control bleeding
  - Have non-specific antipyretic effect
- Increase the antiemetic effect of ondansetron/granisetron/ metoclopramide

Hormones

Estrogens

- Block androgen effects (ex: fosfestrol)
- Used to recruit cells in G0 → G1, so better targets for cytotoxic drugs

Progestogens

(ex: megestrol, medroxyprogesterone)

- Used in endometrial, renal tumors

Hormone Antagonist

- **Tamoxifen**
  - Important in breast cancer treatment
  - Competes with endogenous estrogens for receptor
  - Inhibits transcription of estrogen-responsive genes
  - Blocks the binding of estrogen to receptors of estrogen sensitive cancer cells in breast tissue
- **Flutamide**,
  - cyproterone
  - Important in prostate tumors
  - Androgen antagonists
- **Trilostane**,
  Aaminoglutethimide
  - inhibit sex hormone synthesis at adrenal gland
- **Formestane**
  - inhibits aromatase at adrenal gland

GnRH analogs

- Leuprolide, gosarelin and naferelin
- Effective in management of Prostatic carcinomas
- When given in **constant doses** they inhibit release of pituitary LH and FSH
- These drugs suppress gonadal function due to down regulation and desensitization of Gn-RH receptors

Toxicity:

- Leuprolide may cause gynecomastia, hematuria, impotence and testicular atrophy

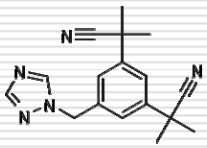
Aromatase inhibitors

- The aromatase reaction is responsible for the extra-adrenal synthesis of estrogen from androstenedione
- This takes place in liver, fat, muscle, skin, and breast tissue, including breast malignancies.
- Peripheral aromatization is an important source of estrogen in postmenopausal women.
- Aromatase inhibitors decrease the production of estrogen in these women.

Aromatase inhibitors

Anastrozole (Arimidex)

- Fourth generation of aromatase inhibitor - effective against ER positive breast cancer
- **Mechanism**:
  - Significantly suppresses serum estradiol levels
  - Inhibits aromatase (CYP19), the enzyme that catalyzes the final step in estrogen production.
- **Toxicity**:
  - rarely severe adverse reactions – some musculoskeletal toxicity

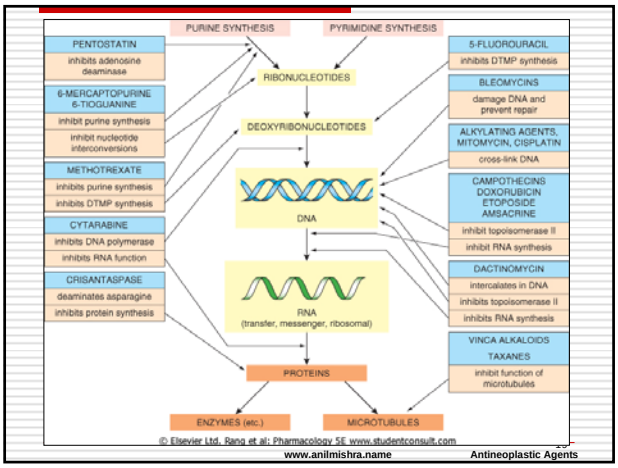


Combination Chemotherapy

Most cancers are/become refractory to treatment by a single agent, combinations of anticancer drugs are often used. The following rules apply to combining drugs in cancer chemotherapy:

1. The drugs each must have some activity against the cancer.
2. The drugs should act via different mechanisms.
3. The drugs should have minimal overlapping toxicity.
4. Cellular resistance to each drug should occur by different mechanisms.

The first drug combination, made famous by Dr. V. DeVita and others at NIH, is called MOPP (Mechlorethamine, oncovonin, procarbazine, and prednisone). MOPP is a curative treatment for Hodgkin's disease and its development was a major step forward.


PURINE SYNTHESIS
PYRIMIDINE SYNTHESIS
PENTOSTATIN
inhibits adenosine deaminase
6-MERCAPTOPURINE
6-TIOGUANINE
inhibit purine synthesis
inhibit nucleotide interconversions
METHOTREXATE
inhibits purine synthesis
inhibits DTMP synthesis
CYTARABINE
inhibits DNA polymerase
inhibits RNA function
CRISANTASPASE
deaminates asparagine
inhibits protein synthesis
RIBONUCLEOTIDES
DEOXYRIBONUCLEOTIDES
DNA
RNA
(transfer, messenger, ribosomal)
PROTEINS
ENZYMES (etc.)
MICROTUBULES
5-FLUOROURACIL
inhibits DTMP synthesis
BLEOMYCINS
damage DNA and prevent repair
ALKYLATING AGENTS, MITOMYCIN, CISPLATIN
cross-link DNA
CAMPOTHECINS
DOXORUBICIN
ETOPOSIDE
AMSACRINE
inhibit topoisomerase II
inhibit RNA synthesis
DACTINOMYCIN
intercalates in DNA
inhibits topoisomerase II
inhibits RNA synthesis
VINCA ALKALOIDS
TAXANES
inhibit function of microtubules
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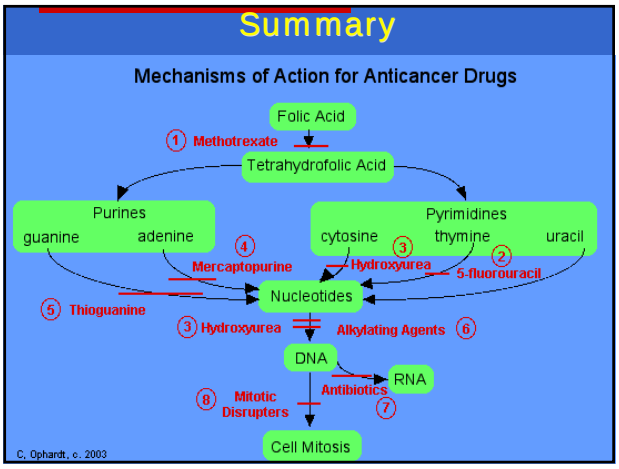
Antineoplastic Agents


Summary
Mechanisms of Action for Anticancer Drugs
Folic Acid
1 Methotrexate
Tetrahydrofolic Acid
Purines
guanine
adenine
Pyrimidines
cytosine
thymine
uracil
4 Mercaptopurine
3 Hydroxyurea
2 5-fluorouracil
Nucleotides
5 Thioguanine
3 Hydroxyurea
Alkylating Agents 6
DNA
RNA
Antibiotics 7
8 Mitotic Disrupters
Cell Mitosis
C, Ophardt, c. 2003