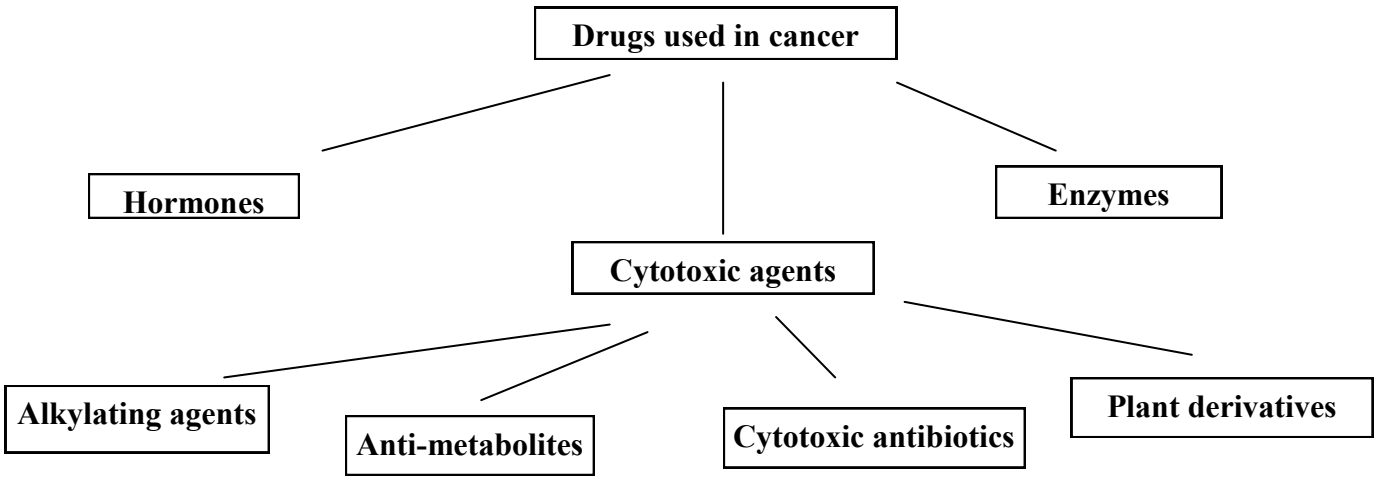
Cancer Chemotherapy

Definition of cancer: loss of normal growth control

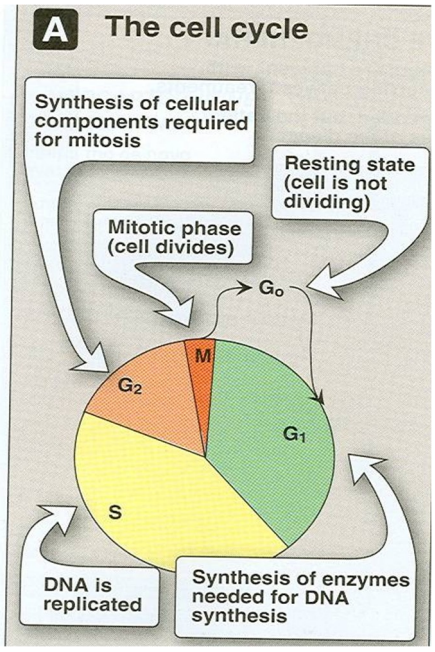
The genesis of cancer cells:
1– activation of proto-oncogenes to oncogenes.
2– inactivation of tumor suppressor genes.

Rationale of chemotherapy:
Cancer chemotherapy strives to cause a lethal cytotoxic event or apoptosis in the cancer cell that can arrest a tumor's progression. (they are anti proliferative)

Which modalities do we use to treat cancer?
- Localized tumors: radiation or surgery
- Metastasis: chemotherapy
- Adjuvant therapy: Surgery + radiation +chemotherapy



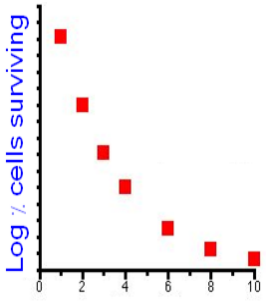
The cell cycle:
The malignant cells are divided to 3 compartments:
- Compartment A: these are cells with active cell division
- Compartment B: in the G_0 phase (dormant cells)
- Compartment C: they're not able to divide.



We divide cancer drugs in relation to cell cycle as:

1. Class 1: cell cycle-nonspecific e.g. alkylating agents (they kill the malignant cell whether they're actively dividing or not)
2. Class 2: cell cycle-specific or phase-specific: we use them as continuous infusion or frequent small doses:

- E..g: hydroxyurea acts on phase S
- Bleomycin acts on late G_2 and M phases

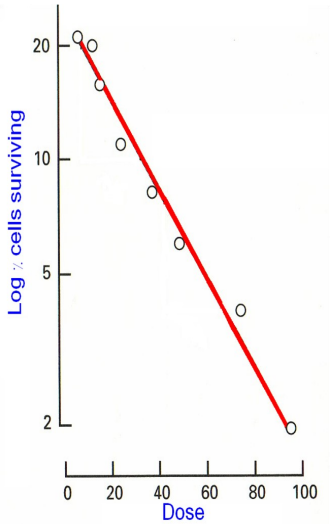


Dose -response for phase -specific drugs

They reach a plateu in cell killing with increasing doses

3. Class 3: cell cycle-specific non phase specific: they're administered as single large doses

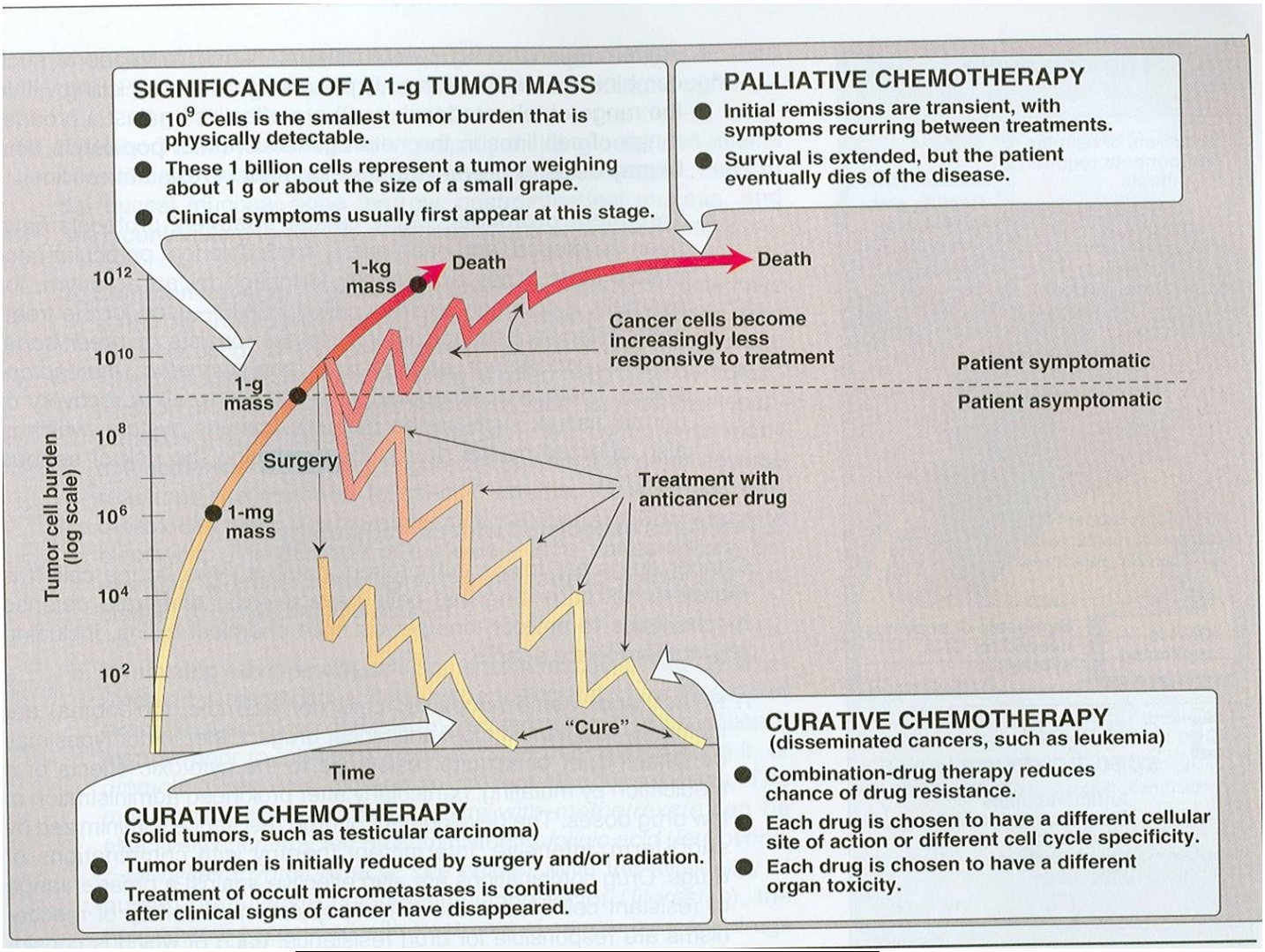
- E..g: anthracycline, antibiotics, chlorambucil, cisplatin.



Their dose response curve follows first order kinetics

Principles of chemotherapy:

- Complete eradication of malignant cells
- Drugs kill a constant proportion of cells rather than a constant number
- Adverse effects are decreased by giving combination of drugs with different toxicities



Don't miss this important figure

Palliation: relief of symptoms caused by cancer and improve the quality of life, even though the drugs may not lengthen life.

The log kill hypothesis:

Let's say there is a tumor with 10^9 cells and there is a drug which kills 99.999% of these cells (remember constant proportion of cells are killed).

So how many cells would remain? The answer is 10000 or 10^4 cells.

This is defined as five-log kill: because $10^9 \div 10^5 = 10^4$

Does this mean we have to stop treatment?

No because the total tumor cells are not eliminated and they may divide and proliferate again and the tumor will recur.

Indication of chemotherapy:

- When neoplasms are disseminated and not amenable to surgery
- Attack micrometastasis after surgery (adjuvant therapy)
- Before surgery to shrink the tumor (neoadjuvant therapy)
- Given in lower doses to assist in prolonging a remission (maintenance therapy)

Treatment regimens:

- Drugs are administered on the basis of body surface area, /m^2
- Drugs with different toxicities, molecular sites, and mechanism of action are combined at full doses
- Drugs with same toxicities are combined by reducing the doses of each

Advantages of drug combination:

- Maximal cell killing with limited toxicity
- Effective against broader range of cells in the tumor
- Prevent the development of resistant cells.

General toxicity of cancer drugs:

- Bone marrow suppression (myelosuppression)
- Loss of hair (alopecia)
- Damage to GI epithelium
- Impaired wound healing
- Depression of growth in children
- Teratogenicity
- Sterility
- Kidney damage (stones)
- Nausea and vomiting
- Caracinogenicity

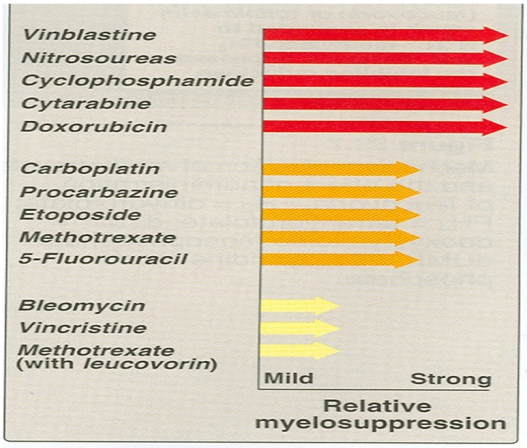


Figure 39.6
Comparison of myelosuppressive potential of chemotherapeutic drugs.

Methods to minimize the side effects:

- Use of cytoprotectant drugs
- Removing some of the patient's bone marrow to reimplant it later
- Diuresis to prevent bladder toxicity
- Use of human granulocyte colony stimulating factor (filgrastim).

alkylating agents

Nitrogen mustards
cyclophosphamide

Alkyl sulfonates
busulfan

Nitrosoureas
Carmustine & lomustine

Mechanism of action:

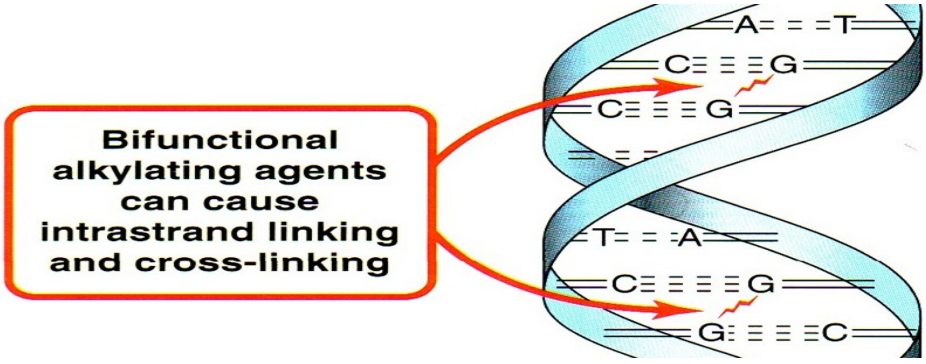
- Alkylating agents act by: transferring their alkyl group to the DNA of tumor cells.
- First: they undergo intramolecular cycliztion to form an ethyleneimonium ion
- Second: they alkylate the N7 position of a guanine nucleotide
- They are bifunctional: they can bind to one guanine or 2 guanine nucleotides

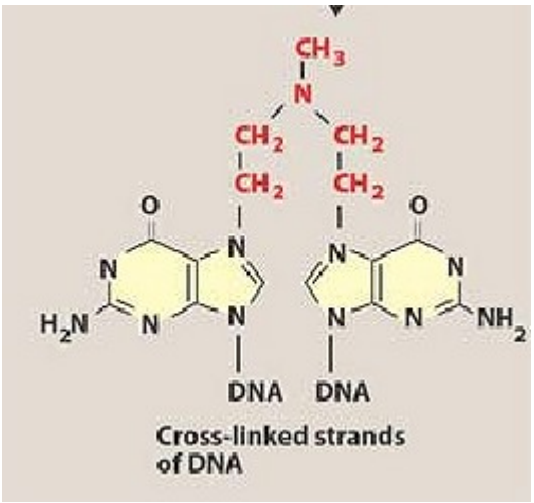
- They can bind 2 guanines in the same strand or both strands

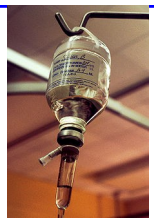
- Alkylation will lead to:

1. Abnormal base pairing with thymidine or
2. Excision of the bound guanine residues

- Cross linkage will lead to the separation or breakage of strands
- Tumor cells are most sensitive in in late G_1 and S phases (but remember they are not cell cycle specific).







Cyclophosphamide

- It's a prodrug
- Activated by liver enzymes P450
- It's converted to aldophosphamide
- Aldophosphamide nonenzymatically gives:

1. Phosphoramide mustard: the active form
2. Acrolein: which gives the side effects of the drug.

Mechanism of resistance:

- Increased DNA repair
- Decreased drug permeability
- Reaction of the drug with thiols

PK

- Given IV or oral
- Metabolites appear in urine

Clinical uses

- Burkitt's lymphoma
- Chronic leukemia
- Myeloma
- Used as immunosuppressent

Adverse effects:

- Nausea & vomiting
- Bone marrow depression
- Veno-occlusive disease of the liver
- Hemorrhagic cystitis:

1. Caused by acrolein
2. Which might be alleviated by ↑ fluid intake and using **mesna** to inactivate acrolein

Busulfan

- Depresses granulocytes and

Platelets at low doses and red cells In high doses.

- No effect on lymphoid tissue and GI
- Taken orally
- Used in chronic granulocyte leukemia
- Associated with: skin pigmentation, pulmonary fibrosis, adrenal insufficiency.

Nitrosourea (lomustine & carmusitne)

PK

- Carmustine is administered IV
- Lomustine taken in the oral form
- They are lipid soluble (can cross the BBB)
- Lomustine is metabolized into active products
- Urinary excretion

Clinical uses

- Tumors of the brain and meninges

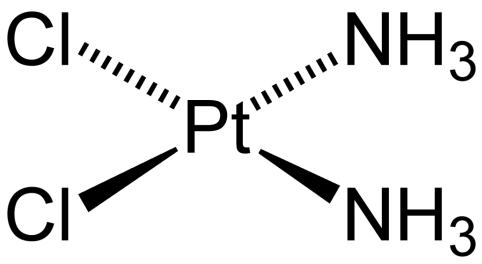
Adverse effects

- Depression of bone marrow starts after 3 weeks of taking the drug.
- Bone marrow depression is **irreversible**
- Renal toxicity & pulmonary fibrosis

Non-cross resistance with other alkylating agents

Streptozocin

- One of the nitrosoureas
- Has minimal bone marrow toxicity
- Used in insulinomas



Cisplatin

- Action is similar to alkylating agents.
- When entering the cell Cl^- dissociates.
- Causes intrastrand and interstrand cross-linking.

PK

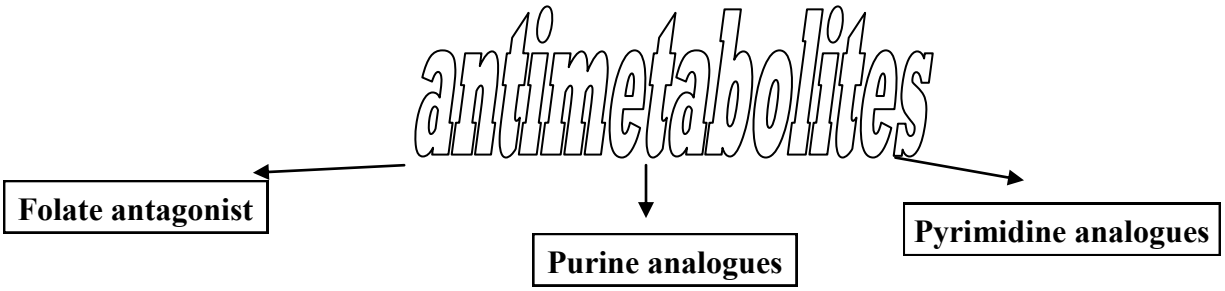
- Given by IV injection or infusion
- 90% is bound to plasma protein
- Little penetration to the CSF
- Excretion by kidneys

Clinical uses

- Testicular carcinoma
- Bladder carcinoma
- Ovarian carcinoma
- Lung cancers
- Esophageal and gastric cancers

Adverse effects

- High nephrotoxicity (reduced by hydration)
- Low myelotoxicity
- Severe nausea & vomiting: —>Use **ondansetron** to treat it
- Tinnitus and hearing loss of high frequency sounds
- Peripheral neuropathy, hyperuricemia, and anaphylactic reaction



Folate Antagonists
Methotrexate

Folate pathway:

Folate $\xrightarrow{\text{Dihydrofolate reductase}}$ FH_2 $\xrightarrow{\text{Dihydrofolate reductase}}$ FH_4

- Then FH_4 will carry 1 carbon to convert dUMP —> dTMP

Methotrexate

Mechanism of action

- It enters the cell competing with folate for its receptor by active transport
- It becomes polyglutamated, thus becoming larger in size and being retained in the cell for a long time.
- It inhibits **dihydrofolate reductase**

PK

- Administered: IV, IM, intrathecal, or oral.
- Excretion of the drug and 7-OH metabolite is through the urine.
- It's a weak acid (add the pH of the urine by giving sodium bicarbonate for rapid excretion).

Clinical uses

- Acute lymphoblastic leukemia
- Burkitt's lymphoma
- Adjuvant in breast carcinoma
- Palliation of metastatic breast, head, neck, cervical.
- Lung carcinoma

Rescue therapy:

- If you want to give high doses of methotrexate you should protect the normal cells.
- Give leucovorin (a form of FH_4) to compensate for depleted FH_4 in the normal cell

Adverse effects

- Depression of the bone marrow
- Damage to the epithelium of the GI
- Pneumonitis
- Nephrotoxicity at high doses.

The drug needs to be monitored
We give higher doses so it can enter the cell with passive diffusion rather than active transport

Pyrimidine analogues
Fluorouracil (5-FU)

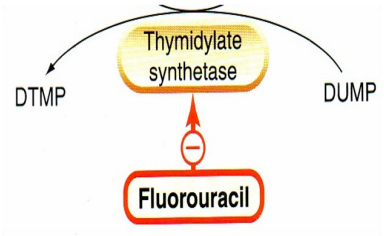
Uracil pathway:

1. Uracil —> dUMP

2. dUMP $\xrightarrow{\text{Thymidylate synthase}}$ dTMP

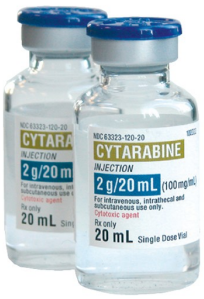
Mechanism of action of fluorouracil:
- 5-FU is a prodrug converted to FdUMP
- It inhibits the action of thymidylate synthase —> "thymineless death"

PK
- Given IV
- Crosses BBB
- $T_{1/2}$ = 10 min
- Excretion through urine
- Adjust dose in hepatic impairment



Clinical uses
- Widely used to treat colorectal cancer as an adjuvant and for advanced diseases
- In combination to treat breast cancer
- Palliative in GI adenocarinoma

Adverse effects
- GI epithelial damage in the form of mucositis and diarrhea
- Myelotoxicity
- Neurotoxicity



Cytarabine

- Cytosine arabinoside
- Acts as pyrimidine analogue

Mechanism of action
- Enter the cell by a carrier
- Undergoes phosphorylation to give cytosine arbinoside triphosphate
- It inhibits **DNA polymerase**
- **S**-phase specific

PK
- Given orally, IV, or intrathecally
- Excretion in the urine

Clinical uses
- Acute myelogenous leukemia & non-Hodgkin's lymphoma
- Intrathecally as alternative to methotrexate in meningeal leukemia or lymphoma

Adverse effects:
- GI epithelium damage
- Nausea & vomiting
- Cerbellar ataxia

Purine Antagonists
fluorouracil

6-Mercaptopurine (6-MP)

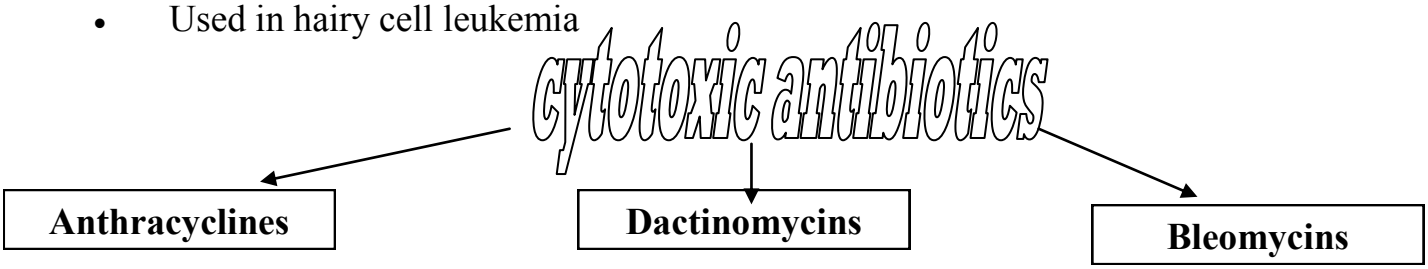
- Used in maintenance therapy of acute lymphoblastic leukemia
- It's a prodrug
- Taken orally
- Doesn't cross the BBB
- Metabolized by the enzyme xanthine oxidase
- Allopurinol (xanthine oxidase inhibitor) will cause accumulation of the drug (be cautious when you give them together)
- When using allopurinol in hematological cancers to treat hyperuricemia, the dose of 6-MP must be reduced.
- Excretion in urine

Fludarabine

- Metabolized to triphosphate which inhibits DNA synthesis (similar to cytarabine)
- Used in chronic lymphocytic leukemia (CLL)
- Myelosuppressive

Pentostatin

- Inhibits adenosine deaminase
- Interfere with purine pathway
- Used in hairy cell leukemia



Doxorubicin

- Anthracylcines:

Mechanisms of action:

1. It binds to DNA and inhibits DNA and RNA synthesis
2. It interferes with topoisomerase II action
3. It binds to cell membrane inhibiting the transport process
4. Produces superoxide ions and hydrogen peroxide (free radical) which cause single strand breaks in DNA

- Heart cells don't have superoxide dismutase or catalase, so this drug exerts significant-**cardiotoxicity**

PK

- IV administration
- Extravasation of the IV infusion on the skin causes cell necrosis
- Doesn't cross the BBB
- Hepatic metabolism
- Excretion majority in bile and little in urine
- Causes red color urine.

Clinical uses

- Carcinomas of breast, ovary, endometrium, bladder, thyroid.
- In combination for lymphoma and Hodgkin's disease.
- Pediatric tumors

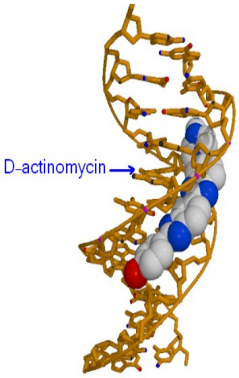
Adverse effects

- Cardiotoxicity: because of free radicals and lipid peroxidation —> Use dexrazoxane to protect the heart
- Bone marrow suppression
- GI disturbance
- Increased skin pigmentation
- Alopecia

Dactinomycin

Mechanism of action

- The drug inserts itself in the minor groove of the DNA between guanosine and cytosine.
- Interferes with the action of RNA polymerase inhibiting DNAtranscription
- It inhibits topoisomerase II



PK

- IV administration
- Doesn't cross BBB
- Most excretion in bile and less in urine

Clinical uses

- Choriocarcinoma
- Testicular tumors
- Lymphoma
- Melanoma
- Sarcoma

Adverse effects:

- Nausea, vomiting, and diarrhea
- Myelosuppression
- Immunosuppression
- Hepatitis
- Extravasation —> skin necrosis

Bleomycin

Mechanism of action

- It forms free radicals
- They break the phosphodiester bond of DNA
- Resulting in strand breakage and release of free bases.
- Most effective in G_2 phase and in non dividing cells

PK

- IV, IM, or SC administration
- Bleomycin-inactivating enzyme is present everywhere except in the lung and skin
- $T_{1/2}$ = 2.5 h
- Excretion by glomerular filtration
- Adjust dose in renal impairment

Clinical uses

- Advanced testicular carcinoma
- Hodgkin's and non-Hodgkin's lymphoma

Adverse effects

- Pulmonary fibrosis—> dose limiting
- Allergic reaction
- Mucocutaneous reaction
- Hyperpyrexia
- It causes **little** myelosuppression

plant alkaloids

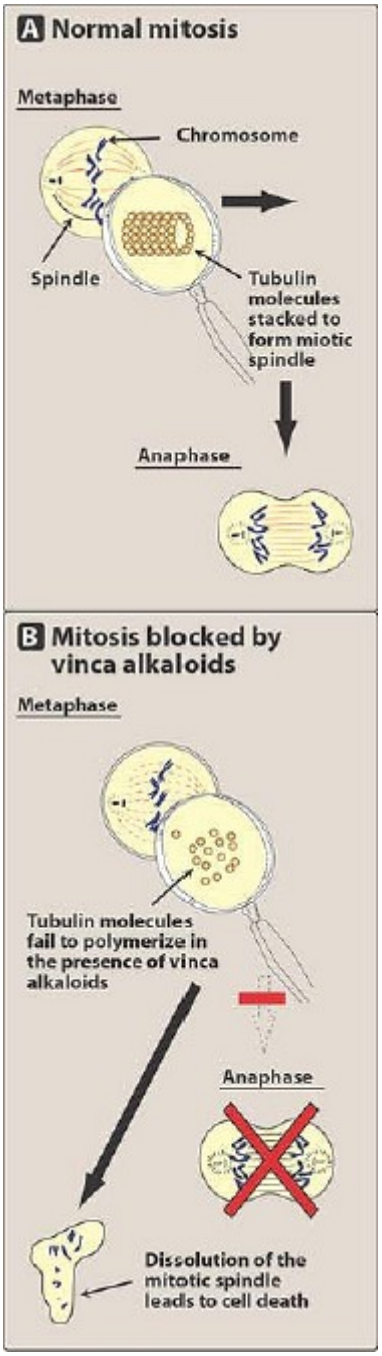
Vinca alkaloids | **epipodophyllotoxins** | **taxanes**

1-Vinca alkaloids

Vincrtistine & vinblastine

Mechanism of action

- They bind to **tubulin**
- They block the tubulin polymerization—> ↓ microtubules
- So the cell will freeze in the M phase and no division will occur



PK

- IV administration
- Causes hyperuricemia so use allopurinol along with it
- Extensively bound to tissues
- Hepatic metabolism
- Biliary excretion
- Adjust dose in hepatic impairment or biliary obstruction

Clinical uses

- Vincristine

1. Acute lymphocytic leukemia
2. Hodgkin's disease
3. Pediatric tumors (Wilm's tumor, neuroblastoma, Ewing's sarcoma, rhabdomyosarcoma)

- Vinblastine

1. Testicular carcinoma
2. Hodgkin's disease
3. Breast cancer
4. Renal cell carcinoma

Adverse effects

- Extravasation causes tissue necrosis and blister formation
- Vincristine: neurological toxicity & SIADH
- Vinblastine: bone marrow toxicity & vesicant (causes blisters)

2-Etoposides

- Derivative of epipodophyllotoxins

Mechanism of action

- Inhibition of topoisomerase II
- Lethal to cells in S and G_2 phases

PK

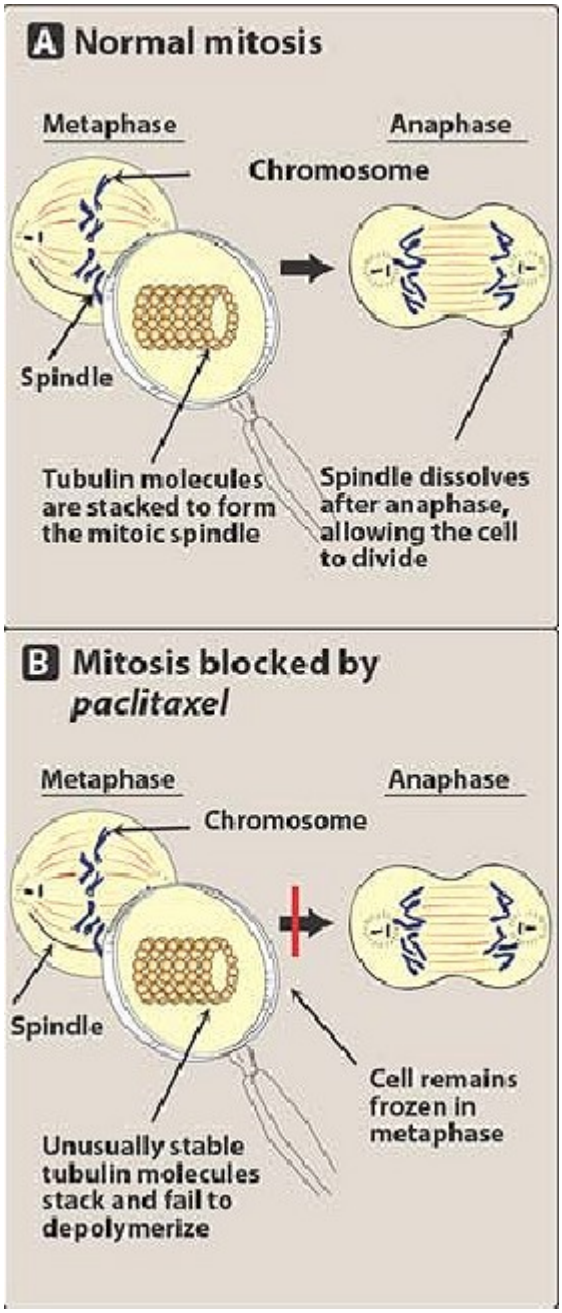
- Oral or IV administration
- Lipid soluble
- 90% protein bound
- Adjust dose in renal impairment

Clinical uses:

- Testicular & ovarian germ cancers
- Lymphoma
- Acute myelogenous and lymphoblastic leukemia
- Lung and gastric cancers

Adverse effects

- Nausea
- Alopecia
- Allergic reaction
- Phlebitis at the site of injection
- Bone marrow toxicity



3-Taxanes

- It derived from the pacific yew tree

Mechanism of action

- They bind to tubulin
- They promote polymerization and stabilization of tubules
- They block disassembly of tubules
- Stable tubules are not functional and thus no division will occur

PK

- Infusion administration
- Large volume of distribution
- Hepatic metabolism (adjust dose in hepatic impairment)
- Biliary excretion

Clinical uses

- Carcinomas of the breast, ovary, lung, head, and neck
- With cisplastin for ovarian and lung carcinoma
- With doxorubicin for breast cancer
- Kaposi's sarcoma

Adverse effects

- Myelosuppression
- Alopecia
- Numbness & tingling sensation

Hormones

- Tumors derived from hormone sensitive tissue may be hormone dependent

Glucocorticoids

- ↓ lymphocyte proliferation —> used in leukemias and lymphomas
- ↓ intracranial pressure

Estrogen

- Estrogen and fosfestrol (prodrug) used in prostatic tumors
- Fosfestrol is activated by phosphatase enzyme
- Estrogen used in breast cancer to recruit cells (cells in compartment B becomes active so other drugs can kill them)

Hormones antagonist

Tamoxifen

- Anti-estrogen

PK

- Taken orally
- Well absorbed
- Maximum plasma levels in 4-6 hours
- Hepatic metabolism
- Biliary excretion

Clinical uses

- Hormone-dependent breast cancers
- Chemopreventive in women with high risk of breast cancer
- Endometrial cancer
- Cardioprotective (↓ LDL oxidation)
- Most effective on post menopausal women

Adverse effects

- Menopausal symptoms
- Fluid retention
- Edema
- Thromboembolic events
- ↑ incidence of endometrial cancer and hyperplasia

Flutamide & cyproterone

- Are NSAIDs
- Bind to androgen receptor and inhibit it
- Orally taken
- Used in prostate tumors

Eznymes

Asparaginase

- It comes from E. coli and Erwinia carotovora
- Hydrolyze Asparagine to Aspartic acid

Mechanism of action

- Tumor cells do not have asparagine synthetase.
- So they depend on external sources of asparagine (from the blood) P.S. human normal cells contain the enzyme asparagines synthetase.
- Asparaginase enzyme decreases asparagine in the blood so tumor cells can't use it.

PK

- IV or IM administration
- Has a low tissue distribution, mainly intravascular distribution
- Little appears in CSF

Clinical uses

- Acute lymphoblastic leukemia & certain types of lymphoma

Adverse effects

- Hypersensitivity & anaphylactic reaction (keep steroid at hand to treat it)
- Urticaria
- Pancreatitis
- Neurotoxicity
- Alterations of clotting factors
- **No** toxicity to bone marrow, GI, or hair follicles

other treatment modalities

immunotherapy

Rationale of immunotherapy

Activates the immune system to act:

1. Indirectly by mediating anti-tumor effects
2. Directly by interrrupting tumor differentiation

Interleukin-2 → induces &/or expands cytolytic T cells against tumors → in metastatic malignant melanoma & renal cell carcinoma

Interferon-α 2b → activates macrophage phagocytic & T cell cytotolytic activities → in hairy cell leukemia, refractory chronic myeloid leukaemia, advanced malignant melanoma & follicular lymphoma.

Immunostimulatory drugs as; Thalidomide → refractory malignant myeloma & Levamisol → adjunctive in colon cancer

Biological Therapy

By recombinant therapy
Monoclonal antibody

By nonrecombinant therapy
Molecular thrapy

- Biological therapy: target specific molecules or cellular processes in the tumor cells.

Monoclonal antibody

How are they prepared?

- Taking the molecular surface of the tumor (cells) and injecting it into a mouse
- The mouse will produce antibodies by a certain B lymphocyte (monoclonal proliferation)
- Take the mouse's lymphocytes and fuse them with human lymphocytes
- Clone the hybrid of these lymphocytes
- Now you have human antibodies against tumor cells, and you can use them for treatment.

Rituximab → against CD20 expressed on lymphocytes→ in β cell lymphoma & chronic lymphocytic leukemia

Bevacizumab → prevents VEGF from acting with receptor so aborts angiogenesis→ to suppress metastasis specially in colorectal & lung cancer / induce shrinkage of breast & renal cancer (causes hypertension, thrombosis, GI perforation, prteinurea, wound healing complication)

Cetuximab → inhibits epidermal growth factor receptor in many carcinomas→ as breast, lung, colon,….. (causes rash and hypersensitivity reactions)

Trastuzumab → HER2/ neu (a special EGFR) expressed on 30% of breast cancer cells → in metastatic breast cancer

Molecular therapy

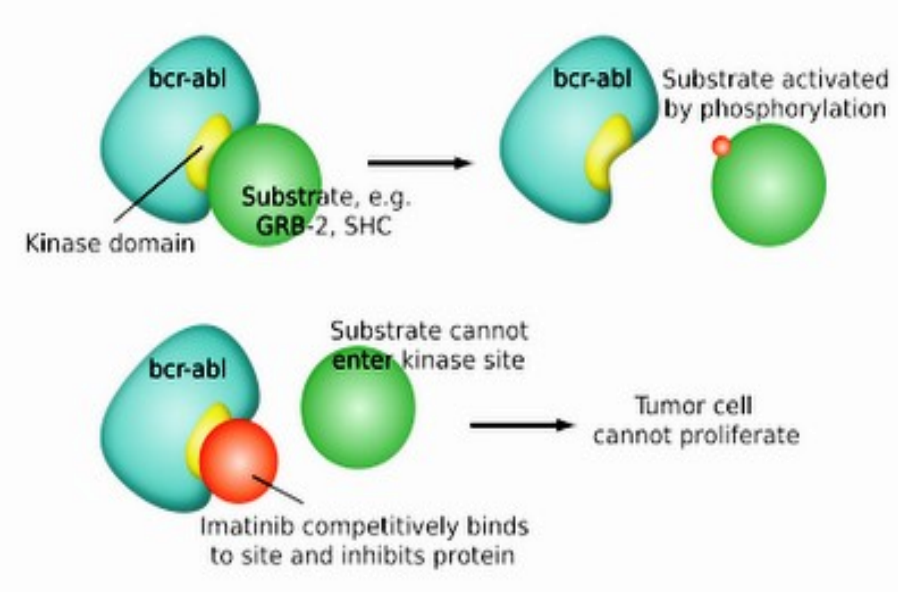
Imatinib (gleevec)

Mechanism of action
It inhibits tyrosine kinase domain of Bcr-Abl oncoprotien & inhibits the receptor for platelet-derived growth factor (PDGF).

PK
Absorbed orally
Highly protein-bound
Hepatic metabolism
Excretion in feces

Clinical uses
Chronic myelogenous leukemia (CML)
GI cancers

Adverse effects
Fluid retention
Diarrhea
Myalgia



Erlotinib *(Tarcevac)* → inhibits TK linked to EGFR → non-small cell lung cancer

Bortezomib *(Velcade)* → Proteosome Inhibitor → inhibit degradation of I_kB → inhibit NF_kB → refractory multiple myeloma

Mechanisms of Tumor Cell Resistance

- Some tumors e.g. malignant melanoma, renal cell cancer, and brain cancer have primary resistance: absence of response from the 1st exposure.

Cellular mechanisms

1. Drug target alteration

- Upregulation of enzyme target e.g. thymidy-late synthase, dihydrofolate reductase
- Enhanced drug metabolism: cytosine arabinoside

2. Multidrug resistance

- ↑ drug efflux via P-glycoprotein transporters e.g. doxorubicin, paclitaxel, vincristine, etoposide
- Drug conjugation by glutathione e.g. 6-mercaptopurine & cyclophosphamide
- ↓ inward transport e.g. methotrexate
- ↓ production of methotrexate polyglutamates
- Overexpression of the **multidrug resistance protein 1(MRCP1)** —> ↑ resistance to natural drugs

3. Enhanced survival

- Suppression of apoptosis
- Enhance DNA repair system e.g. cyclopospha mide & cisplatin

Non-cellular mechanisms

3. Pharmacological sanctuaries

- Blood brain barrier
- Solid tumors

3. Altered in vivo growth kinetics

- Non dividing cells in hypoxic regions
- Tumor repopulation between treatment

You can add verapamil to inhibit P-glycoprotein and ↓ resistance