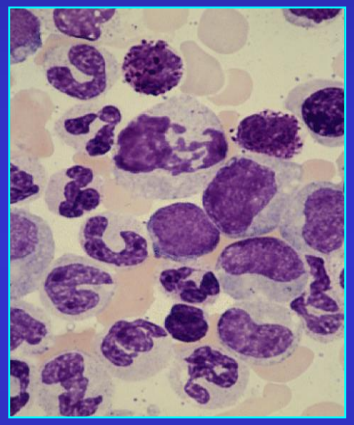
CHEMOTHERAPEUTICS OF MALIGNANT DISEASES



J. Mojžiš

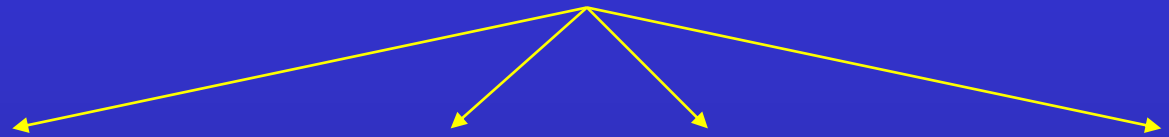
The outcome of cancer therapy

- 1900: survival rates for sarkoma, carcinoma and haematological cancers less than 10%
- 2000: more than 50%
  - Childhood Acute lymphoblastic leukemia : > 70%
  - Hodgkin disease: > 90%
  - Survival rates remain low for pancreatic (4%), liver (7%), glioblastoma (5%), lung (15%)
  - Prostate and breast cancers have 5-year survival rates better than 80%, **but respond poorly at later stages**
- Major improvment in diagnosis and therapy (chemotherapy and supportive therapy)

Carcinogenesis

DNA mutation

- **hereditary**
- **acquired**



radiation viruses chemicals drugs

Categories of genetic changes resulting in malignity

a) inactivation of tumor supressor genes:

- **mutation**
- **binding to a virus protein**
- **binding to a mutated cellular protein**

b) activation of protooncogenes to oncogenes (if mutated = oncogenes):

- **point mutation (single nucleotide polymorphisms-SNPs)**
- **gene amplification**
- **chromosome translocation**
- **virus interaction**

Important oncogenes

These genes contribute to unregulated cell division if they are present in a mutant oncogenic form.

The mutant proteins often retain some of their capabilities but are no longer sensitive to the normal control mechanizms.

HER-2/*neu* (*erb*B-2): a growth factor receptor
ras: a signal transduction molecule
myc: a transcription factor
src: a protein tyrosine kinase
hTERT: an enzyme that functions in DNA replication.
Bcl-2: a membrane associated protein that functions to prevent apoptosis.

Important tumor suppressors

Tumor suppressors produce products that inhibit the division of cells if conditions for growth are not met (DNA damage, a lack of growth factors or defects in the division apparatus). A key to understanding tumor supppressors is that it is the LOSS OF FUNCTION of these genes that leads to problems:

p53 (*TP53*): a transcription factor that regulates cell division

Rb: alters the activity of trancription factors and therefore controls cell division

APC: controls the availability of a transcription factor

BRCA: involved in DNA repair.

Oncogenes – autonomy of cell growth

Oncogenes interfere with:

- **mechanisms of proliferation**
- **mechanisms of differentiation**

by means of:

- **production & secretion of autocrine growth factors**
- **receptors for growth factors**
- **cytosolic & nuclear signal pathways**
- **transduction systems controling cell cycle**

Cancer types

categorized based on the functions/locations of the cells from which they originate:

- **Carcinoma:** a tumor derived from epithelial cells, those cells that line the surface of our skin and organs (80-90% of all cancer cases reported)
- **Sarcoma:** a tumor derived from muscle, bone, cartilage, fat or connective tissues.
- **Leukemia:** a cancer derived from white blood cells or their precursors.
- **Lymphoma:** a cancer of bone marrow derived cells that affects the lymphatic system.
- **Myelomas:** a cancer involving the white blood cells responsible for the production of antibodies (B lymphocytes).

Characteristics of cancer cells

1) Excessive autonomous cell growth

- tumor cells produce growth factors that stimulate their own proliferation (i.e. autocrine stimulation)
- malfunction in cell regulatory systems (i.e. abnormal receptors signal cell division in absence of growth factor)
- loss of growth inhibitory signals (i.e. contact inhibition)

(2) Invasiveness

- ability to grow into adjacent tissue

(3) Ability to metastasize

- spread to new sites and form new growths
- lack of cell-cell contact inhibition (i.e. disorderly migration over adjacent cells)
- production of enzymes that degrade protein barriers
- production of growth factors that stimulate angiogenesis

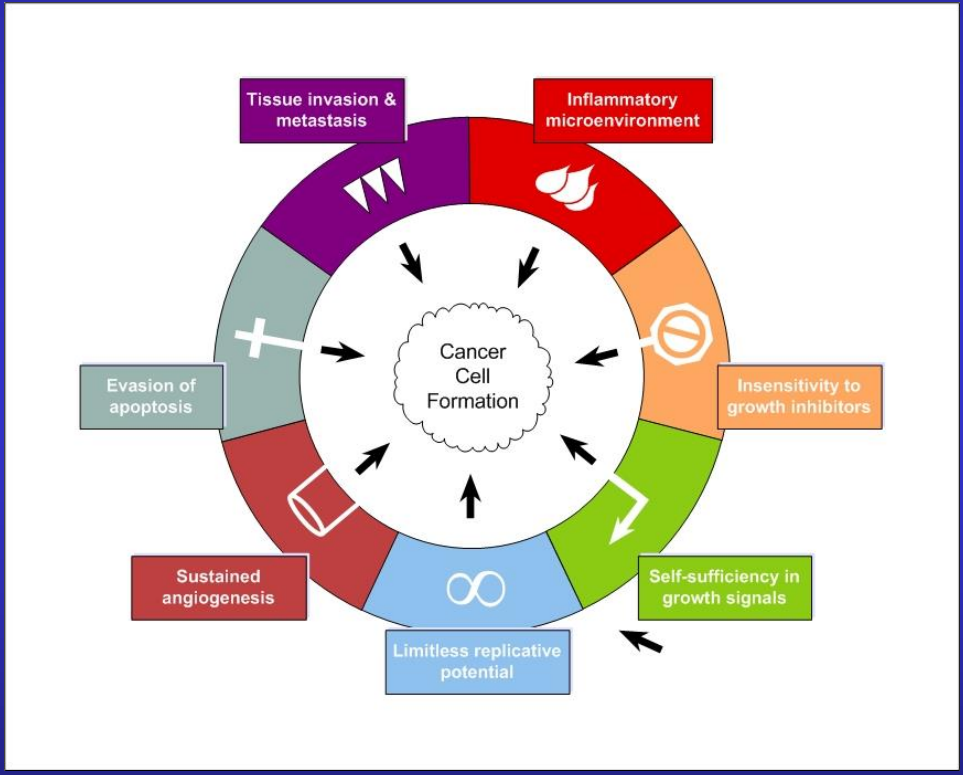
Characteristics of cancer cells *– cont.*

(4) Defective differentiation and immortality

- related to uncontrolled proliferation (i.e. differentiated cells don't divide)
- loss of function
- failure of cancer cells to undergo programmed cell death

(5) Genetic instability

Cancer hallarks



An introduction to cancer treatments

- the treatment given for cancer is highly variable and dependent on the type, location and amount of disease and the health status of the patient
- the treatments are designed to either:
  - directly kill/remove the cancer cells or
  - to lead to their eventual death by depriving them of signals needed for cell division or
  - the treatments work by stimulating the body's own defenses.

Classical types of cancer treatment

Often in combination, either simultaneously or sequentially:

- **Surgery:** Often the first line of treatment for many solid tumors. If the cancer is detected at an early stage, surgery may be sufficient to cure the patient.

- **Radiation:** The goal of radiation is to kill the cancer cells directly by damaging them with high energy beams.

Classical types of cancer treatment

- **Chemotherapy:** A term used for a wide array of drugs used to kill cancer cells. Chemotherapy drugs work by damaging the dividing cancer cells and preventing their further reproduction.
- **Hormonal Treatments:** These drugs are designed to prevent cancer cell growth by preventing the cells from receiving signals necessary for their continued growth and division.

New types of cancer treatment

- **Specific Inhibitors:** Drugs targeting specific proteins and processes that are limited primarily to cancer cells or that are much more prevalent in cancer cells (*imatinib – PTK inh.)*
- **Antibodies:** The antibodies used in the treatment of cancer have been manufactured for use as drugs (trastuzumab, bevacizumab).

New types of cancer treatment

- **Biological Response Modifiers:** The use of naturally occuring, normal proteins to stimulate the body's own defenses against cancer (interferons).

- **Vaccines:** Stimulate the body's defenses against cancer. Vaccines usually contain proteins found on or produced by cancer cells. By administering these proteins, the treatment aims to increase the response of the body against the cancer cells (HPV vacc.)

Sensitivity of tumours to chemotherapy

- chemosensitive tumours
- intermediary chemosensitive tumours
- chemoresistant tumours

Chemosensitive tumours

- **generally sensitive to several drugs**
- **combined chemotherapy is prefered**
- **chemotherapy is always indicated**
- e.g. ALL in children, Hodgkin d., ca testes, ovarian ca

Intermediary chemosensitive tumours

- **complete remission rate about 10%**
- **high partial response (about 50%)**
- **combined chemotherapy is slightly more effective**
- **chemotherapy could be used**

  (no as first-choice therapy)
- e.g. adult AML, multiple myeloma, neuroblastoma, prostate ca, breast ca, endometrial ca

Chemoresistant tumours

- **low response rate (about 20%)**
- **complete remission is rare**
- **chemotherapy has only adjuvant role**
- **neoadjuvant therapy**
- e.g. pancreatic ca, bile-duct and blader ca, Grawitz tu, colorectal ca

Factors influencing chemotherapy response

- **fraction of proliferating cells**
- **cell cycle rate**
- **synchronisation of cell cycle within tumour**
- **tumour mass**
  large tumours are relatively less sensitive:
  1. a lot of cells in G0 2. ↓ penetration of drugs
- **kinetics of cell killing**
  cytotoxic drugs kill only a part of cells of certain type
- **resistance of tumour cells**

Mechanisms of resistance I.

- **Defect activation**
  - ***cyclophosphamide* needs metabolic activation**
  - ***metothrexate* needs conversion to *MTX*-polyglutamate in cells**
- **Increased inactivation**
  - **sulfhydryl substances - glutathion, metalothionein – scavenge reactive molecules**
  - **aldehyde dehydrogenase – inactivation of *cyclophosphamide***
- **Increased nucleotide levels**
  - **can affect the effectiveness of antimetabolites**
- **Changes in DNA repaire**
  - **⇑ repaire mechanisms, elimination of cross-links**
  - ***bleomycine &* other DNA-interfering drugs**

Mechanisms of resistance II.

- **Changes in target structure**
  - **active enzyme with lower drug affinity: DFR-*metothrexate***
- **Reduced quantity of target structure**
  - **⇓ amount of Topo II: *etoposide***
- **Gene amplification**
  - ***metothrexate*: ⇑ DFR requires more MTX to block the activity**

Mechanisms of resistance III.

- **Decreased accumulation**
  - **Decreased uptake**
    - ***MTX* - ↓ protein transporter**
    - ***melphalan*/leucine transport**
  - **Increased efflux**
    - **multidrug resistance (MDR):**

      - most often for natural drugs *doxorubicine, etoposide, actinomycine D, vinca alcaloids*

      - Pgp is normally expressed in some cells, e.g. stem cells in bone marrow

Combination chemotherapy

- tumours have tendency to be **resistant to some drug** (cell heterogeneity)
- resistance is often appeared during therapy with **only one drug** (proliferation of mutated cells)
- **several sites of effect** are possible with drugs with different side effects
- **cummulative biochemical damage** appear in cancer cells

Practical use of anticancer drugs

- the doses are expressed in

mg per m^2

of body surface

(more precise dose/effect ratio)

General rules of chemotherapy

- Adjuvant therapy: courses of cytostatic drugs are given when the cancer has apparently been destroyed by surgery or radiotherapy. Its objective is to eradicate micrometastases.
- Neoadjuvant therapy: is defined as a preoperative cytostatic treatment in patients with locally advanced solid tumors; The aims of neoadjuvant chemotherapy + radiotherapy are: the potentiality of curative resection, the reduction of surgical measures, and an increase in life span.

General rules of chemotherapy

Supportive therapy:

- **Antiemetics (5-HT_3 -antagonists)**
- **Antibiotic prophylaxis and therapy (febrile neutropenia)**
- **Prophylaxis of urate nephropathy (allopurinol)**
- **Enteral and parenteral nutrition**
- **Pain – analgesic drugs**
- **Psychological support**

- **Supportive therapy to reduce toxicity**
  - **hematotoxicity – bone marrow transplantation, hematopoietic growth factors**
  - **Specific antagonists: antifolate (methotrexate) – folate (leucovorin)**
  - **MESNA - donor of –SH groups, decreased urotoxicity of cyclophosphamide**
  - **dexrazoxane: chelates iron, reduced anthracycline cardiotoxicity**
  - **amifostine: reduces hematotoxicity, ototoxicity and neurotoxicity of alkylating agents**

Toxic effects of anticancer chemotherapeutics

- myelotoxicity
- alopecia
- loss of appetite & weight
- nausea & vomitus
- taste change
- stomatitis, esophagitis, constipation, diarrhea
- fatigue
- cardiotoxicity
- neurotoxicity
- lung damage
- sterility & teratogenicity
- hepatotoxicity & nefrotoxicity
- ↓ wound healing
- ↓ growth (children)
- carcinogenicity

Bone marrow supression (myelotoxicity)

most common side effect

⇩ RBC, WBC, and platelets

a) leukopenia

infections (fever, cough, congestion of nose, tremor)

prophylactically ATB

hemopoetic growth factors (GM-CSF, G-CSF)

b) anemia (dizziness, headache, tachycardia, tachypnoe)

erythropoetin (growth factor)

c) trombocytopenia (bleeding, gum bleeding, disturbancies in coagulation)

transfusion of platelets

Bone marrow supression

Drugs with high potential for myelotoxicity:

vinblastine, cyclophosphamide, iphosphamide, cisplatin, etopozide, paklitaxel, nitrosoureas

Drugs with low potential for myelotoxicity:

vincristine, bleomycine

Loss of hair

- it appears 2-3 week after therapy begining
- rapid growing hair folicules
- after therapy termination – hair appear again
- changes in color and quality of hair

Emesis

- direct irritation of stomach
- inderectly – irritation of nerve ending
- acute – minutes-hours after drug administration
- delayed – 24 hours – several days after therapy
- waited (anticipatory nausea) – before application of antineoplastic agents
- cisplatin, dacarbazine, cyclophosphamide, doxorubicine

Emesis

- ondasetron, granisetron (inhibitors of 5-HT_3-receptors) most effective treatment available for prevention of severe vomiting
- metoclopramid (inhibitor of D_2 receptors)
- lorazepam (BZD)- good for anticipatory nausea and vomiting before cancer therapy
- dexametazon (during the first 24 hours)
- cannabinoids – delayd emesis?
- neurokinin-1 antagonist (aprepitant) – prevention
- dexamethasone and aprepitant - prevention of delayed emesis

Chemotherapy induced emesis

Acute	Delayed	Anticipatory
The intensity peaks after 2-6hrs, occurs more often and tend to be more severe than delayed emetic episodes	Peak incidence occurring at 48-72h. Commonly found with cisplatin, carboplatin, cyclophosphamide, doxorubicin	After a negative past experience with chemotherapy; 10-60% incidence rate

Emetogenic potential of antineoplastic agents

EMETOGENIC POTENTIAL	TYPICAL AGENTS	DEFINITION
High	Cisplatin Dacarbazine Nitrogen mustard	Emesis in nearly all patients
Moderate	Carboplatin Anthracyclines Cyclophosphamide Irinotecan	Emesis in >70% of patients
Low	Mitoxantrone Taxanes	Emesis in 10%–70% of patients
Minimal	Hormones Vinca alkaloids Bleomycin	Emesis in < 10% of patients

ACUTE NAUSEA AND VOMITING

Emetic risk group	Antiemetics
High	Serotonin antagonist + dexamethasone + aprepitant
Anthracycline + Cyclophosphamide (AC)	Serotonin antagonist + dexamethasone + aprepitant
Moderate (other than AC)	Serotonin antagonist + dexamethasone
Low	Dexamethasone
Minimal	No routine prophylaxis

The Antiemetic Subcommittee of MASCC. Ann Oncol 2006;17:20-28.

ESMO Minimum Clinical Recommendations. Ann Oncol: in press.

DELAYED NAUSEA AND VOMITING

Emetic risk group	Antiemetics
High	Dexamethasone + aprepitant
Anthracycline + Cyclophosphamide (AC)	Aprepitant or dexamethasone
Moderate (other than AC)	Dexamethasone A serotonin antagonist may be used as an alternative
Low	No routine prophylaxis
Minimal	No routine prophylaxis

The Antiemetic Subcommittee of MASCC. Ann Oncol 2006;17:20-28.

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Obstipation/Diarhoea

Obstipation

generaly consequence of opioid application

⇩ of water intake, ⇩ in daily activities

dehydratation

Diarhoea

75% patients

damage of gastric mucosa (rapidly dividing cells) ⇨ dehydratation, malnutrion, electrolyte disbalance

5-FU, docetaxel

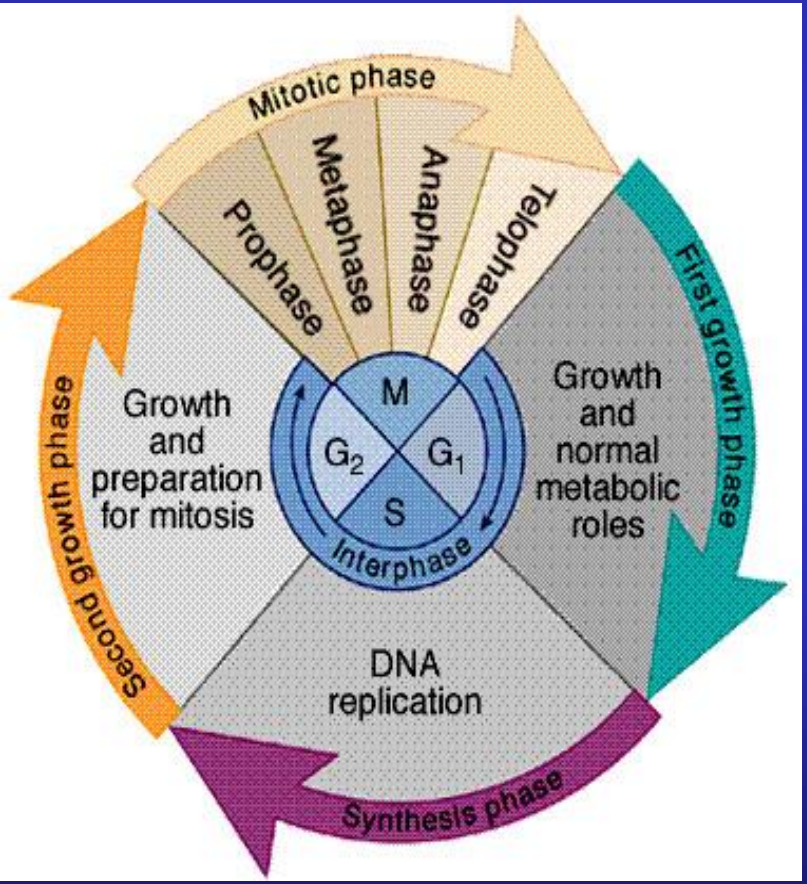
Cardiotoxicity

- doxorubicin, daunorubicin (10% of patients)
- acute, subacute, chronic
- free radicals
- dexrazoxane

ANTICANCER DRUGS

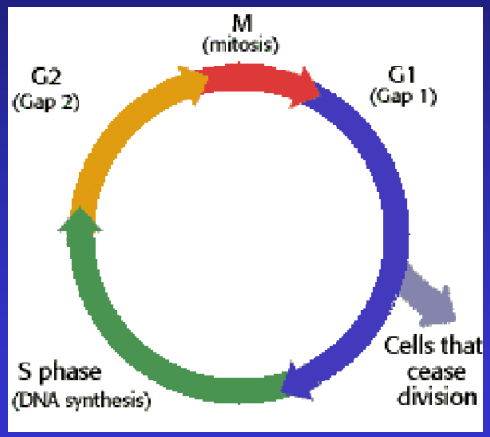
Mechanism of action - cell cycle

- intercalation
- blockade of metabolic steps in DNA synthesis
- ↓ of enzymes regulating cell cycle
- ↓ RNA synthesis
- ↓ protein synthesis
- ↓ microtubular functions



Cell cycle

Gap 0 (G0): There are times when a cell will leave the cycle and quit dividing. This may be a temporary resting period or more permanent. An example of the latter is a cell that has reached an end stage of development and will no longer divide (e.g. neuron).



Gap 1 (G1): Cells increase in size in Gap 1, produce enzymes needed for DNA synthesis

- **S Phase: To produce two similar daughter cells, the complete DNA instructions in the cell must be duplicated. DNA replication occurs during this S (synthesis) phase.**

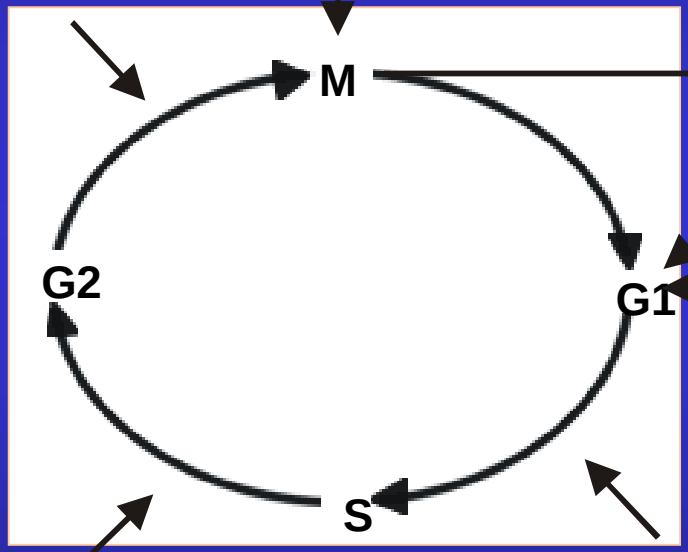
- **Gap 2 (G2): It is the gap between DNA synthesis and mitosis, the cell will continue to grow and produce new proteins & RNA.**

- **Mitosis or M Phase: Cell growth and protein production stop at this stage in the cell cycle. All of the cell's energy is focused on the complex and orderly division into two similar daughter cells.**

The cell-cycle and phase specificity of some cytotoxic drugs

Vincristine, Vinblastine
Paclitaxel, Docetaxel

Cyclophosphamide
Bleomycin
Actinomycin D



Hydrocortisone

G_0 = resting phase
G_1 = prereplicative phase
G_2 = postoperative phase
S = DNA synthesis
M = mitosis or cell division

Purine antagonists
Methotrexate
Cyclophosphamide
5-Fluorouracil
Cytosine arabinoside
Daunomycin

Actinomycin D
5-Fluorouracil
Cytosine arabinoside
Methotrexate
6-Mercaptopurine
6-Thioguanine

The cell-cycle and phase specificity of anticancer drugs

- **Class 1 agents (non cell cycle specific):** proliferation independent or nonspecific: kill cells whether they are proliferating (G_1 - M) or not (G_0) nonspecific cytotoxicity ie. kill both normal and malignant cells to same extent eg. alkylating agents carmustine
- **Class 2 agents (cell cycle specific - phase specific)**: only toxic to neoplastic cells in certain phase of cell cycle, reach a plateau in cell killing with increasing dosages, eg. hydroxyurea is toxic to cells in S-phase, bleomycin is toxic to cells in G2 and early M-phase, vinca alkaloids, taxanes are toxic to cells in M-phase
- **Class 3 agents (cell cycle specific - non-phase specific)**: proliferation dependent, cycle specific, kill proliferating neoplastic cells in preference to resting cells, single large doses eg. anthracycline antibiotics, chlorambucil, cisplatin

Chemotherapy: classification based on the mechanism of action

- **Antimetabolites:** Drugs that interfere with the formation of key biomolecules including nucleotides, the building blocks of DNA.
- **Genotoxic Drugs:** Drugs that alkylate or intercalate the DNA causing the loss of its function.
- **Plant-derived inhibitors of mitosis:** These agents prevent proper cell division by interfering with the cytoskeletal components that enable the cell to divide.
- **Plant-derived topoisomerase inhibitors:** Topoisomerases unwind or religate DNA during replication.
- **Other Chemotherapy Agents:** These agents inhibit cell division by mechanisms that are not covered in the categories listed above.

Antimetabolites

- An antimetabolite is a chemical with a similar structure to a metabolite required for normal biochemical reactions, yet different enough to interfere with the normal functions of cells, including cell division.
- All antimetabolites are used in cancer treatment, as they interfere with DNA production and therefore cell division and the growth of tumors (mainly in S-phase specific).

- They are classified into:

1- Folic acid analogues

2- Purine analogues

3- Pyrimidine analogues

- Purin and pyrimidine antagonists are phosphorelated inside the body into nucleotid form in order to be cytotoxic

Methotrexate

- 1948 Sidney Farber (Children's Hospital Boston) used FA as a supportive therapy of children with leukemia
- Later he attempted folate deprivation. The numbers of leukemia cells decreased = the idea of cytostatic drugs – antifolates
- 1-rst derivative aminopterine = first succesfull short-term remissions of ALL in children, excesive toxicity
- Discovery of the mechanism of action of aminopterine.
-
- Methotrexate designed as an DHFR inhibitor.
- Marketed in 1953.

Methotrexate- cont.

- A folic acid analogue, prevents the formation of tetrahydrofolate, essential for purine and pyrimidine synthesis, by inhibiting dihydrofolate reductase (DHFR), an enzyme that reduces folic acid to its active reduced form.
- This leads to inhibition of production of DNA, RNA and proteins (as tetrahydrofolate is also involved in the synthesis of amino acids as serine and methionine).
- It is actively taken up into the cells by the same transport system for folate (resistance…..?)
- The most common toxicity is nepherotoxicity (pptn of the drug in renal tubule.)

Methotrexate- cont.

Indications:

- (medium to high doses)
  - Acute lymphocytic leukemia
  - Large cell lymphoma
  - High grade lymphoma
  - Head and neck cancers
  - Breast cancers
  - Bladder cancers

- Low-dose MTX: immunosuppressive therapy of psoriasis, rheumatoid arthritis, Crohn disease…

Side effects

- **myelosuppression, GIT, pneumonitis, nephrotoxicity** (tubular precipitation - hydratation); leukovorine
-

Resistance to Methotrexate

There are three known ways in which a cell may acquire immunity to the effects of this folate antagonist:

- Decreased concentration of the drug in the cell (decreased influx, increased efflux, decreased polyglutamate synthesis/increased hydrolysis)
- Amplification of the DHFR gene causes an increase in the amount of DHFR present and has been shown to correlate with reduced response to methotrexate treatment.
- Mutations in DHFR that reduce DHFR-methotrexate binding

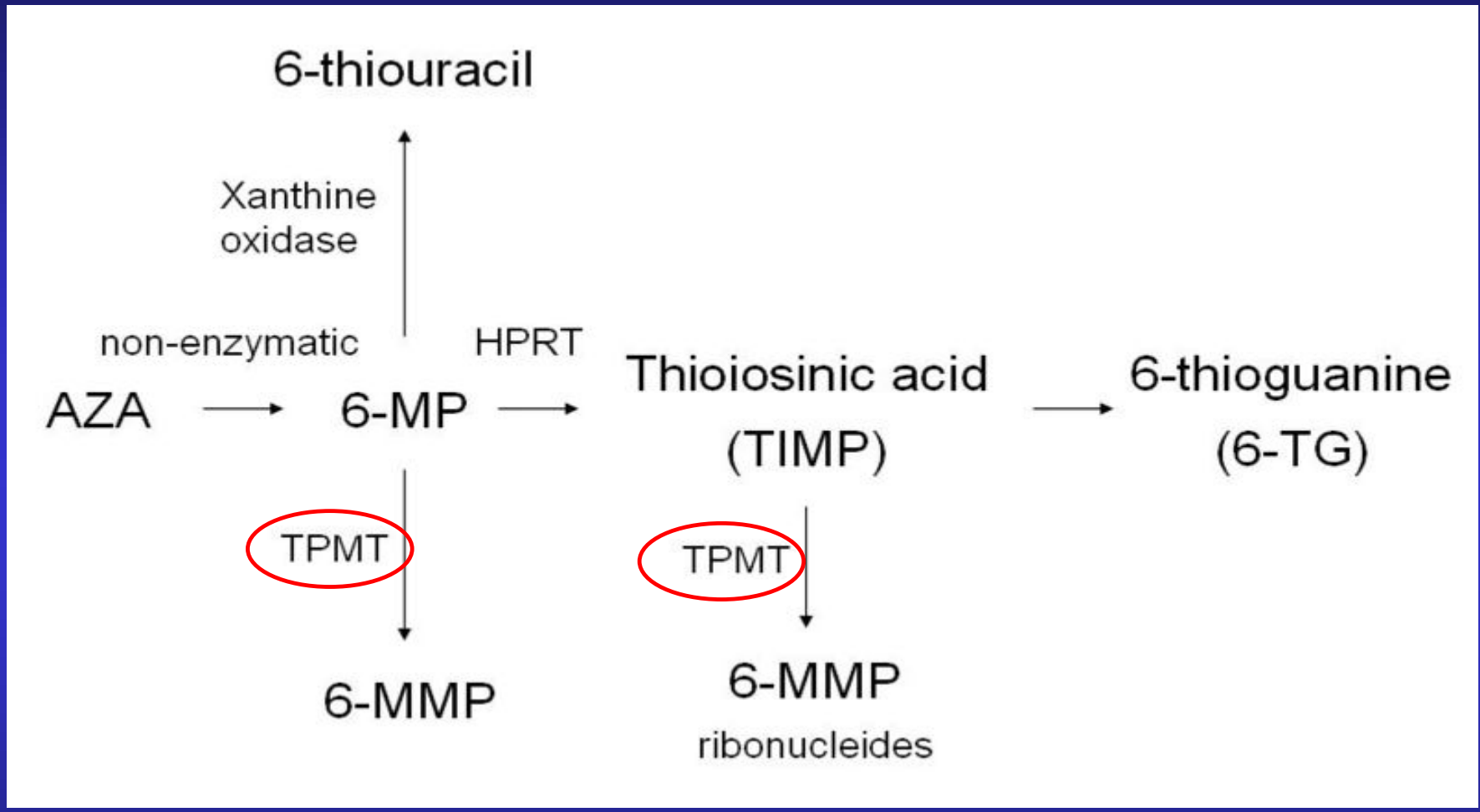
Purine analogues

- 6- mercaptopurine
- 6- thioguanine

6-mercaptopurine

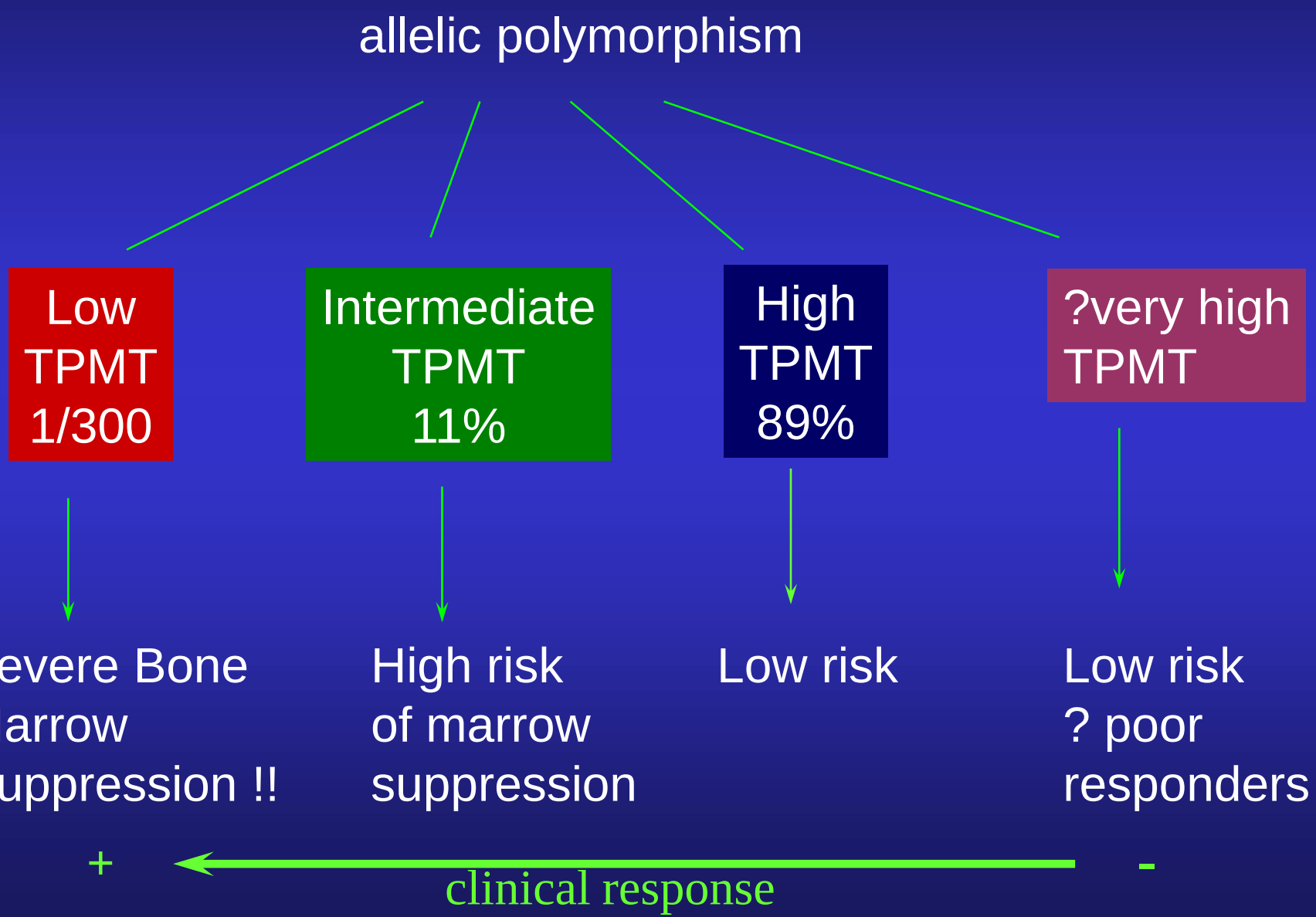
- It is acts as a purine analogue and once enter the cell, it is converted to 6-TGN 6-MP-ribosephophate and can be incorporated into RNA and DNA resulting in non functioning RNA and DNA - finally inducing cell cycle arrest and apoptosis.
- It is used to treat leukemia, pediatric non-Hodgkin's lymphoma
- Adverse effects: myelosuppression (leukopenia, thrombocytopenia), GIT (diarrhea, vomiting, pain), reversible hepatotoxicity
- Azathioprine (prodrug of 6-MP): immunosuppressive therapy (Crohn dis., after transplantation, lupus erythematodes, glomerulonephritis etc.)

Metabolism of 6-mercaptopurine



Patients with an inactive enzyme TPMT (thiopurine methyltransferase) due to genetic polymorphism are at high risk of life-threatening toxicity (myelosuppression). Genetic test for TPMT mutation or evaluation of TPMT activity in erythrocytes help to reduce risk (starting dose is reduced 10-fold in poor metabolizers)

TPMT (thiopurine methyl transferase)



Pyrimidine analogues

- 5-flurouracil (5-FU)
- Gemcitabine
- Capecitabine
- Cytosine arabinoside (Ara-C)

5-fluorouracil

- metabolized to the nucleotide fluorouridine monophosphate (5-FUMP)

- 5-FUMP is further metabolized to
  - A/ the triphosphate 5-FUTP which is incorporated in DNA
  - B/ 5-fluorodeoxyuridine monophosphate = a strong inhibitor of thymidilate synthetase

- inhibition of DNA synthesis **(Not RNA or protein)**
- finally – induction of cell cycle arrest and apoptosis by inhibiting the cell's ability to synthesize DNA.
- It is an S-phase specific drug

5-fluorouracil - cont

Indications:

- Breast cancer, pancreatic cancer, stomach cancer, colorectal cancer, genito-urinary tract cancers (anus, adrenal gland, bladder, cervix, endometrium, ovaries, penis, prostate, and vulva) …..

Adverse effects:

- Nausea and diarrhea, myelosupression (may lead to anemia), mouth sores, pigmentation changes in the skin

Cytosine Arabinoside (Cytarabine)

- Cytidine analog (arabinose instead of ribose)
- Cytarabine triphosphate is incorporated in DNA and blocks its function.
- Inhibitor of DNA and RNA-polymerases and nucleotide reductase

Indications:

Acute non-lymphocytic leukemia, ALL, CML

Side effects:

Bone marrow suppression, anorexia, nausea and vomiting, diarrhea, oral inflammation or ulceration, rash, fever

Gemcitabine

•Gemcitabine is an antimetabolite that acts as a pyrimidine analog. It is incorporated into a dividing cell's DNA which causes the cell to undergo apoptosis.

Indications:

NSCLC (in combination with cisplatin), pancreatic cancer (advanced or metastatic)

Side effects:

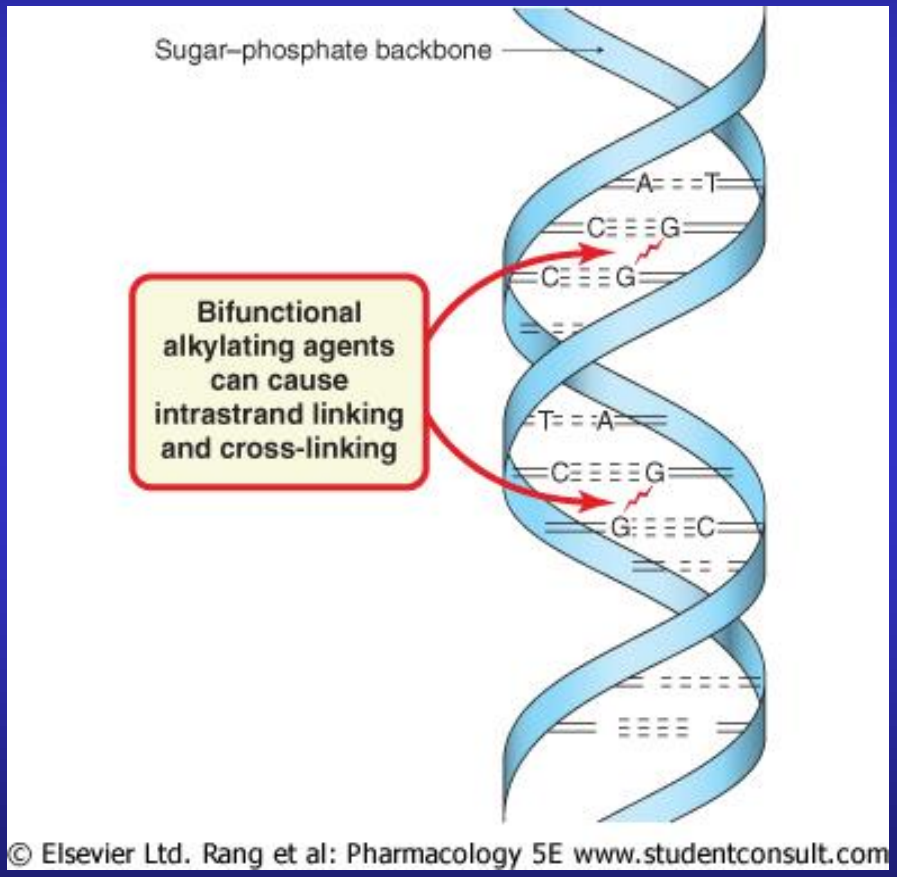
•Flu-like symptoms, fever (within 6–12 hours of first dose), fatigue, nausea (mild), vomiting, allergic reaction, hair loss

Alkylating agents

The first class of chemotherapy agents used.

- These drugs work by alkylation with nucleophilic substitution - most importantly **DNA**.
- They stop tumour growth by cross-linking guanine nucleobases (N7 of guanine) DNA double-helix strands - directly attacking DNA.
- This makes the strands unable to uncoil and separate.
- As this is necessary in DNA replication, the cells can no longer divide.
- The net result is cancer cell undergo apoptosis.

Alkylating agents



Alkylating agents

- largest class of anticancer agents - commonly used drugs

5 subgroups:

1) nitrogen mustards - cyclophosphamide, melphalan, chlorambucil,
2) alkyl sulfonates - busulfan
3) nitrosoureas - carmustine, lomustine
4) aziridines - temozolomide
5) platinum compounds – cisplatin, carboplatin, oxaliplatin

Cyclofosfamide

- It acts as cytotoxic and immunosuppressor agent.
- Prodrug - must be activated by the CYP 450 system, which turns it into a nitrogen mustard.
- most widely used alkylating agent

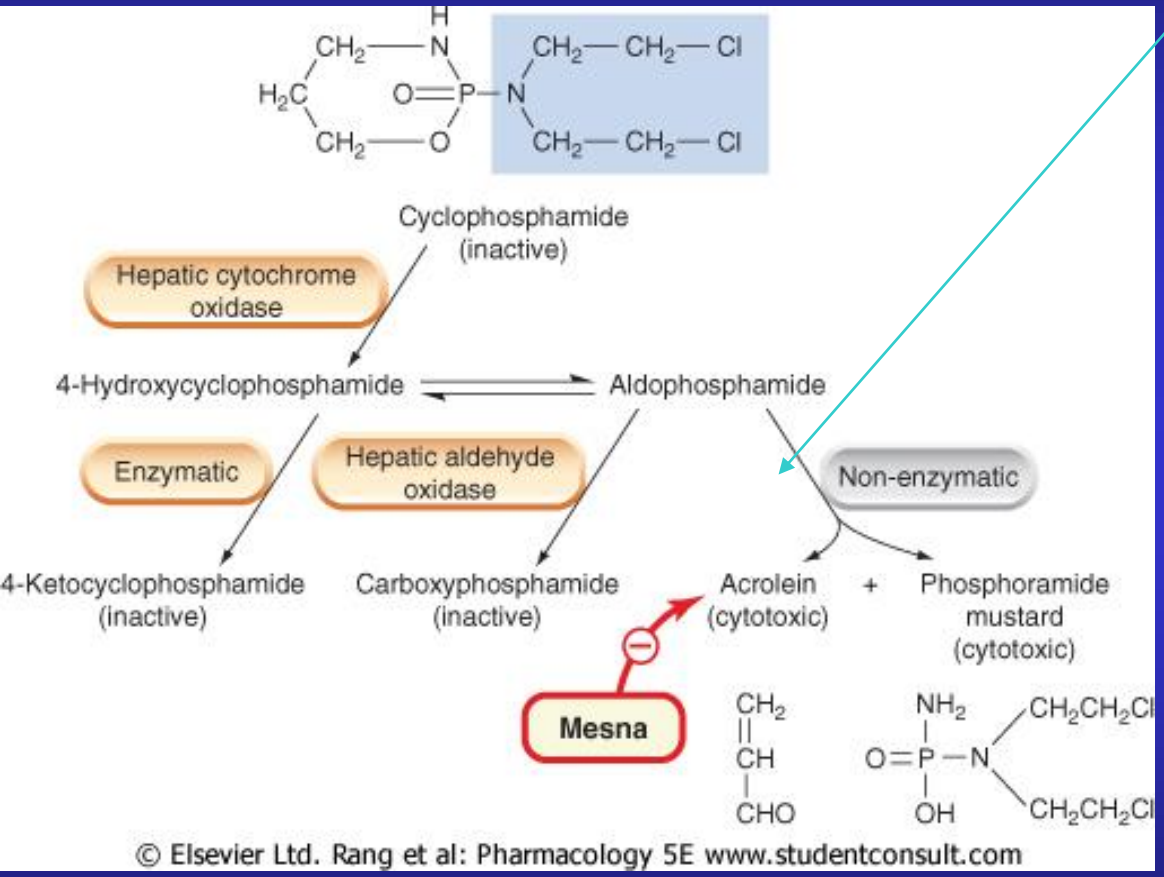
Indications:

- Hodgkin's Disease, Non-Hodgkin's lymphoma, tumors of head, neck, ovaries, and breast
- used in combination with methotrexate, doxorubicin or fluorouracil as adjuvant therapy post breast cancer surgery

Side Effects:

- myelosupression, severe nausea and vomiting, acute hemorrhagic cystitis, sterility, hypersensitivity reactions

Treatment of cyclofosfamide toxicity



Acrolein - **hemorrhagic cystitis**

Prevention: hydratation

Treatment: MESNA (donor of –SH group – non-toxic thioeters

Busulfan

- alkylating agent that forms DNA-DNA intrastrand crosslinks between the DNA bases G and A and between G and G
- Prevention of DNA replication, apoptosis

Indications:

chronic myelogenous leukemia (CML) and other leukemias, lymphomas, and myeloproliferative disorders

Side effects:

interstitial pulmonary fibrosis ("Busulfan Lung"), myelosupression, hyperpigmentation, seizures, emesis, wasting syndrome

Carmustine

– is able to form interstrand crosslinks in DNA, which prevents DNA replication and DNA transcription.
– lipophilic, enter CNS

Indications:

several types of brain cancer (including glioma, glioblastoma multiforme, medulloblastoma and astrocytoma); multiple myeloma and lymphoma (Hodgkin's and non-Hodgkin).

Side effects:

Myelosupression, pulmonary toxicity

Temozolomide

- alkylation/methylation of DNA, which most often occurs at the N-7 or O-6 positions of guanine residues
- methylation damages the DNA and triggers the death of tumor cells

Indications:

Grade IV astrocytoma, melanoma

Side effects:

nausea and vomiting, genotoxicity

Cisplatin

forms crosslinks within DNA strands. *Cis-platin is not really an "alkylating" agent, but since it operates via the same mechanism as the alkylating agents, it is placed within that group.*

Indications:

- **Very powerful against TESTICULAR CANCER**
- **Also good for carcinomas of ovary, bladder, head, and neck**

Cisplatin – cont.

Side effects:

- **nephrotoxicity (minimized via massive hydration; ROS)**
- **myelosuppression**
- **GIT toxicity**
- **emetogenity (aprepitant + ondansetron + dexamethasone - better for highly emetogenic chemotherapy than just ondansetron and dexamethasone.**
- **ototoxicity (no effective treatment to prevent this side effect)**
- **neuropathies**
- **electrolyte disturbance**: ⇩ Mg, K, Ca

Carboplatin

Indications:

Germ cell tumors, ovarian cancer, H&N cancer , SCLC, NSCLC, bladder cancer, endometrial cancer, relapsed and refractory (resistant to ordinary treatment) acute leukemia

Side effects:

- Myelotoxicity (Decreased white blood cell count with increased risk of infection, Decreased platelet count with increased risk of bleeding)
- Altered kidney function (at high doses)

Oxaliplatin

Indications:

Oxaliplatin is primarily used in the treatment of metastatic or recurrent colorectal cancer.

Side effects:

- Neuropathy
- Tiredness, weakness
- Diarrhea
- Nausea and vomiting
- Abdominal pain
- Fever
- Loss of appetite

Cytotoxic ATB

- **Anthracyclines**

(daunorubicine, doxorubicine, epirubicine, idarubicine)

- **Bleomycines**

Anthracyclines

- Anthracycline antibiotics rank among the most effective anticancer drugs ever developed
- DOX and DNR were isolated from the pigment-producing *Streptomyces peucetius* early in the 1960s

- MOA:
  - **Intercalation**: between the bases of DNA and blocks DNA synthesis and transcription.
  - **Enzyme inhibition**: the drug inhibits the activity of an enzyme, **topoisomerase type II**.
  - Formation of iron-mediated **free oxygen radicals** that damage the DNA and cell membranes (effect ?, adverse effects)

Anthracyclines – cont.

- Doxorubicin is useful in a wide range of cancers and only a few cancer types are unresponsive to the drug.

Indications:

- Doxorubicin is commonly used to treat Hodgkin's disease, breast cancer, lung cancer, soft tissue sarcoma, multiple myeloma, ovarian cancer

- Epirubicin: similar to doxorubicin

- Daunorubicin shows much narrover spectrum of activity: acute lymphoblastic or myeloblastic leukemias

- Multidrug resistance to all anthrycyclines

Anthracyclines – cont.

Side effects:

- Acute: nausea, vomiting, and heart arrhythmias, mzelosupression, alopecia.

- Chronic: cardiomyopathy and congestive heart failure; related to a patient's cumulative lifetime dose.

- epirubicin or idarubicin exhibit improvements in their therapeutic index, but the risk of inducing cardiomyopathy is not abated.
  - Dexrazoxane is a cardioprotectant agent that is sometimes used to reduce the risk of cardiotoxicity.
  - ROS

Bleomycine

(glycopeptide ATB-radiomimetic)

- Fe ion chelatation, interaction with O_2
- superoxide & hydroxyl radicals
- degradation of preformed DNA
- chain fragmentation
- radiomimetic effect
- most effective in G_2 & M phase, as well as G_0

- testicular tumors & malignant lymphomas
- orofacial tumors, ca vulvae, penis, skin
- i.v., i.m.

Side effects

- shivering, fever
- lung fibrosis
- allergies, mucocutaneous reactions
- low hemat. tox.

Plant alkaloids

Mitosis inhibitors

- **Vinca alcaloids** *(vincristine, vinblastine, vinorelbine)*
- **Taxans** *(paclitaxel, docetaxel)*

TOPO inhibitors

- **TOPO I** *(topotecan, irinotecan,)*
- **TOPO II (***etoposide, teniposide)*

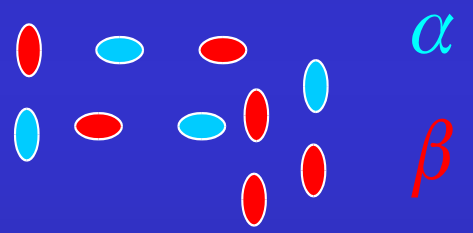
Mitosis inhibitors

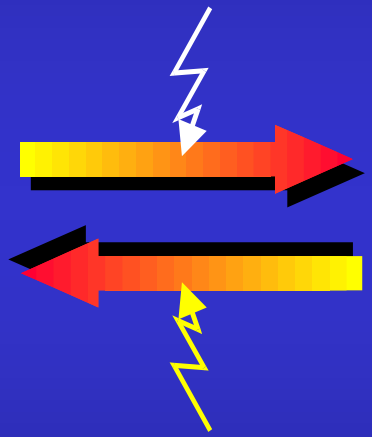
Mechanism of action

Inhibition of polymerisation:

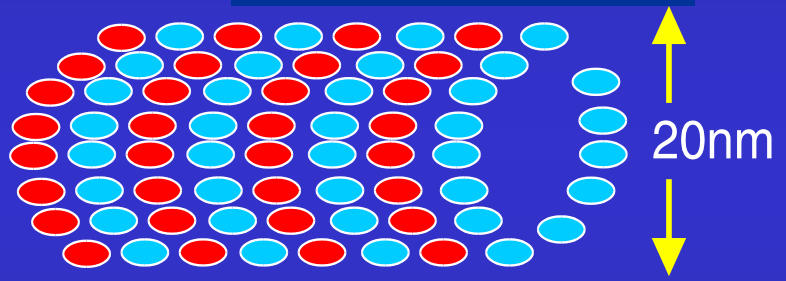
- colchicin
- vinca alcaloids

Tubuline





Microtubulus



Stimulation of polymerisation

Inhibition of depolymerisation

- taxans

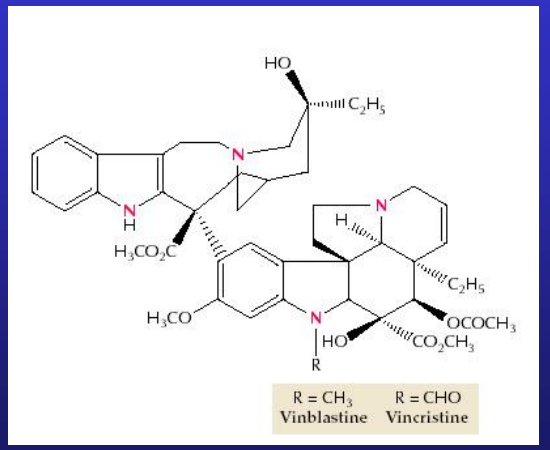
Vincristine (vinblastine, vinorelbine)

Mechanism of action

- inhibition of tubuline polymerisation
- inhibition of mitotic spindle formation
- effective in G_2/M phase

Side effects

- myelosuppression
- ⇓ phagocytosis, chemotaxy of leukocytes
- ⇓ axonal transport in neurons
- paresthesies, neuromuscular abnormalities



Vincristine, vinblastine

Indications

Vincristine

- ALL & AML
- Hodgkin lymphoma, NHL
- multiple myeloma
- combination therapy in some solid tumors

Vinblastine

- Hodgkin lymphoma, NHL
- testicular tumors
- choriocarcinoma
- Grawitz tumor

Paclitaxel, docetaxel

Mechanism of action

- microtubular stabilisation
- final effect like vinca alcaloids

Kinetics

- very low water solubility
- only as i.v. perfusion

Paclitaxel, docetaxel

Side effects

- **myelosuppression**
- **neurotoxicity**
- **hypersensitivity**

(premedication with steroids & antihistaminics)

Indications

- **metastatic tumors (breast)**
- **progressive ovarial tumors**
- **NSCLC**
- **Kaposi sarcoma** (AIDS)

Topoisomerase inhibitors

- Topoisomerase I inhibitors irinotecan and topotecan derived from kampthotecin
- Topoisomerase II inhibitors etoposide and teniposide – derivatives of podophylotoxin
- Both type I and type II topoisomerases change the supercoiling of DNA. Topoisomerases unwind or religate DNA during replication.

Camptothecin derivatives

More than 30 years ago it was found that extracts from a Chinese tree, Camptotheca Acuminata, had potent anticancer activity against a mouse leukemia. The active substance, designated Camptothecin, was tried clinically, but was too toxic.

Topotecan (irinotecan)
(topo I inhibitors)

Mechanism of action

- **topo I inhibition**
- **its levels are ↑ during the whole cell cycle**

Side effects

- **diarrhea, reversible myelosuppression**
- **relatively low toxicity**

Indications

- **SCLC (first line) metastatic ovarial tumors in case of first line therapy failure *(topotecan)***
- **colorectal ca in progress *(irinotecan)***

Topoisomerase II inhibitors

- Synthetic Podophyllotoxin derivatives: etoposide, teniposide
- Podophyllotoxin is a non-alkaloid toxin present in the rhizome of American Mayapple Podophyllum peltatum (mandrake)

Etopozide (tenipozide)

Mechanism of action

- **TOPO II inhibition**
- **Inhibition of mitochondrial functions & nucleoside transport**

Side effects

- **nausea, vomitus**
- **myelosuppression, alopecia**

Indications

- **solid tumors**

  (lung-SCLC, testicular, ovarial, urinary blader, glioblastoma multiforme)

- **malignant lymphoma, acute non-lymphatic leukemia**

Hormonal Treatment

- Cancer arising from certain tissues, including the mammary and prostate glands, may be inhibited or stimulated by appropriate changes in hormone balance.
- Some forms of breast, ovarian and prostate cancer are subject to hormonal treatments.
- The idea behind the majority of hormone-based cancer treatments is to starve the cancer cells of the hormonal signals that would otherwise stimulate them to divide.
- The drugs used in these treatments work by blocking the activity of the hormone in the target cell.

- Some newer treatments are designed to prevent the production of the hormone, cutting off the signal at the start.

- The hormonal treatments are often combined with surgery and/or radiation and/or chemotherapy. In these situations, the hormonal treatments are referred to as an 'adjuvant' treatment.

Corticosteroids

Corticosteroids have broad use in cancer treatment. Some are used to treat adult leukemias, adult lymphomas, and acute childhood leukemia.

Immunosuppressive mechanism

- Glucocorticoids suppress the cell-mediated immunity.
- Inhibition of the cytokines interlukin and TNF-γ sznthesis.
- The inhibition of cytokine production reduces the T cell proliferation.
- Glucocorticoids also suppress the expansion

The most common corticosteroids used in cancer treatment are: · dexamethasone, hydrocortisone, · methylprednisolone

Breast Cancer - Selective Estrogen Receptor Modulators (SERMs)

- In 1992, tamoxifen became the first SERM to be used for the treatment of breast cancer.

- While it does decrease estrogenic effects in the breast, it unfortunately has a pro-estrogenic activity in the uterus, causing a rise in uterine cancer for tamoxifen-treated breast cancer patients.

- Recently, next generation SERMs such as raloxifene have been investigated for their potential as breast cancer treatments. This drug appears to have anti-estrogenic effects in both breast and uterine tissues.

Tamoxifen (toremifen)

Mechanism of action

- nonsteroidal antiestrogene
- inhibits estradiol binding to receptors

Indications

- p.o. appl. in breast cancer with positive estrogene receptors

Side effects

- metrorhagies
- thrombophlebitis
- flush
- alopecia
- estrogene endometrial effect

Aromatase inhibitors

- After menopause, women produce a consistent low level of estrogen that is derived from androgen precursors. These precursors are converted to estrogen through the actions of the enzyme aromatase.

- By blocking the action of this enzyme, aromatase inhibitors prevent the formation of estrogen.

- There are two types of aromatase inhibitors that have been approved as treatment for postmenopausal women with estrogen-receptor positive metastatic breast cancer:
  - steroidal inhibitors such as exemestane and
  - non-steriodal inhibitors (anastrozole and letrozole).

Prostate Cancer - Specific Androgen Receptor Modulators (SARM's)

- testosterone and dihydroxytestosterone bind to specific receptors in the cells of the prostate - regulate the growth of the prostate cells.
- In cancer cells, this regulation is compromised.
- The androgens bind to the receptors in cancer cells and contribute to their growth and division.
- Anti-androgen molecules via the preferential binding to the androgen receptors, prevent the androgens from binding and therefore reduces their pro-growth activities.
  - Flutamide, Bicalutamide

Flutamide

oral, non-steroidal antiandrogen drug primarily used to treat prostate cancer.

Side effects:

Hepatotoxicity, gynecomastia, GIT discomfort, muscle wasting, osteoporosis

Enzymes

Enzymes

- Asparaginase is an enzyme that breaks down asparagine which is needed for cell maintenance and growth.

- In many cases of leukemia, unlike normal cells, the leukemia cells are unable to make their own asparagine and must rely on outside sources of asparagine for survival.

- By depleting free asparagine in the body, which is necessary for cancer cell survival asparaginase treatment results in a depletion of cancerous cells while normal cells are more likely to be preserved.

Asparaginase

Indications:

- i.m., i.v. in ALL

Side effects:

- weak myelosuppression, GIT toxicity & alopecia
- nausea, vomiting, CNS depression, anaphylaxis, hepatotoxicity

PTK inhibitors

(imatinib mesylate)

Mechanism of action, kinetics, indications

- **PTK inhibition**

- **⇓ phosphate group transport from ATP & phosphorylation of tyrozine residues in substrate proteins**
- **Inhibition of transduction signals transmission**
- **p.o. appl. in therapy of CML & GIST**

Side effects

- **nausea, vomiting, diarrhea**
- **edema, headache & muscle pain**
- **neutropenia & thrombocytopenia**

IX. Monoclonal antibodies

(rituximab, trastuzumab)

Rituximab

- **monoclonal antibody only for i.v. appl.**
- **indicated in lymphoma therapy**

Trastuzumab

- **monoclonal antibody only for i.v. appl.**
- **indicated in HER2 Neu positive breast ca therapy**

Side effects

- **pseudoinfluenza sy.**
- **fever**
- **headache, chest, abdominal, muscle & joint pain**
- **nausea, vomiting, diarrhea & exanthema**

Bevacizumab

Anti-VEGF **MAb** (only i.v. application)

- ´treatment of **metastatic colorectal ca, renal ca, ovarial ca, cervical ca, NSLC, glioblastoma**

Mechanism of action

- Inhibiton of new blood vessels growth
- Regresion of newly formed cancer vascular bed
- ⇩ vascular function and tumor perfusion

Adverse reactions:

- GI perforation, serious bleeding, ⇩ wound healing, increase of BP