اللهم إنا مغلوبون فانتصر

اللهم انصر اخواننا المرابطين الحقايلين في إدلب وفي غزة

* حرب عقيدة

Cancer Chemotherapy

Drugs for Leukemias and Lymphomas

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With her notes written by

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focus on → special side effect
↳ MOA

there might be questions like matching etc...

* We will focus more in drug that used in hematopeotic malignancy → leukemias, lymphomas
* Cancer is second leading cause of death following Cardiovascular diseases.

Cancer Chemotherapy

↳ Scientific concept by german Scientist (بول ايرليخ) in 1907 which was discribe medicine that target specifically & efficiently disease without harming the body

- "Magic bullet" drug, is a dream that did not materialize yet. → our target in chemotherapy
- Cytotoxic drugs are given in repeated courses arranged so that the recovery of normal cells can occur, but little recovery of cancer cells is possible.

The Ideal Anticancer Drugs

Modern drug discovery, we are trying to define the differences between normal & cancer cells → target cancer cell without affecting normal one ⇒ less side effects.

- Exploits the differences between normal and tumor cells. Currently, Recent development in Cancer discovery focus on inhibitors of metabolic Pathways exploited by cancer cells only.
- Broad spectrum of activity. so this mean the drug is going to kill many types of cancers
- Good distribution through the body. so it can reach different parts of the body where different types of cancer is exist.
- Non-immugenic.
- Adequate biological half life.
- Reasonably priced.

* as oppossed to conventional cancer therapy or cytotoxic therapy
  - which include
    - Radiation
    - Chemotherapy

new term was emerged which is **targeted therapy** → does not immediatly kill cancer cells as conventional therapy but slow the cancer metabolism.

Targeted therapy: type of cancer treatment that targets proteins that control how the cancer cells grow, divid and spread. also, it can alters or slow the cancer metabolism which leads to

- interruption of the cancer cell growth
- inhibiting glucose uptake of cancer cell with time.
- regress the tumor which occurs in many days or months

*Ultimitly, cancer cells which treated with targeted therapy will going to die.

Current Anticancer Drugs drawback

So the same drug treat one type of cancer & increase the risk of another type.

- Carcinogenic.
- Mutagenic. ⇒ cause mutation
- Teratogenic. ⇒ High chance of getting teratogenicity in pregnant women in the upcoming fetus.
- Immunosuppressive.
- Very toxic, but tolerance can develop.

↳ luckly

* theraputics index gives us an indecation about the safty of the drug. & it is a ratio between the dose that is toxic to the dose that is effective.

Cancer Chemotherapy - basics

- Anticancer drugs have a small therapeutic index.
- They produce toxic side effects.
- Know the toxicities. → in order to choose appropriate treatment → prevent as much as we can of these toxicity
- Drug combinations - use ones that have different mechanisms and different toxicities.
- Drug cycles - Visible tumor = 1g or 10^9 cells. Each cycle of therapy kills less than 99% of the cells, so multiple cycles are necessary to kill all tumor cells.

So there is 1% of the cancer cells remain untreated or unkilled which is 10^9 cells & don't forget cancer cells replicate very fast

Cancer Chemotherapy - basics

Rapidly dividing cells are most susceptible -

- cancer cells
- bone marrow
- hair follicles
- intestinal epithelium

Slow growing tumors are less or unresponsive because chemotherapy affecting Rapidly dividing cells more than others.

- (colon and lung cancer)

↳ slow growing tumors

Cell Cycle

both normal & tumor cells

but neoplastic tissue may differ in the number of cells that is in various stages in the cell cycle

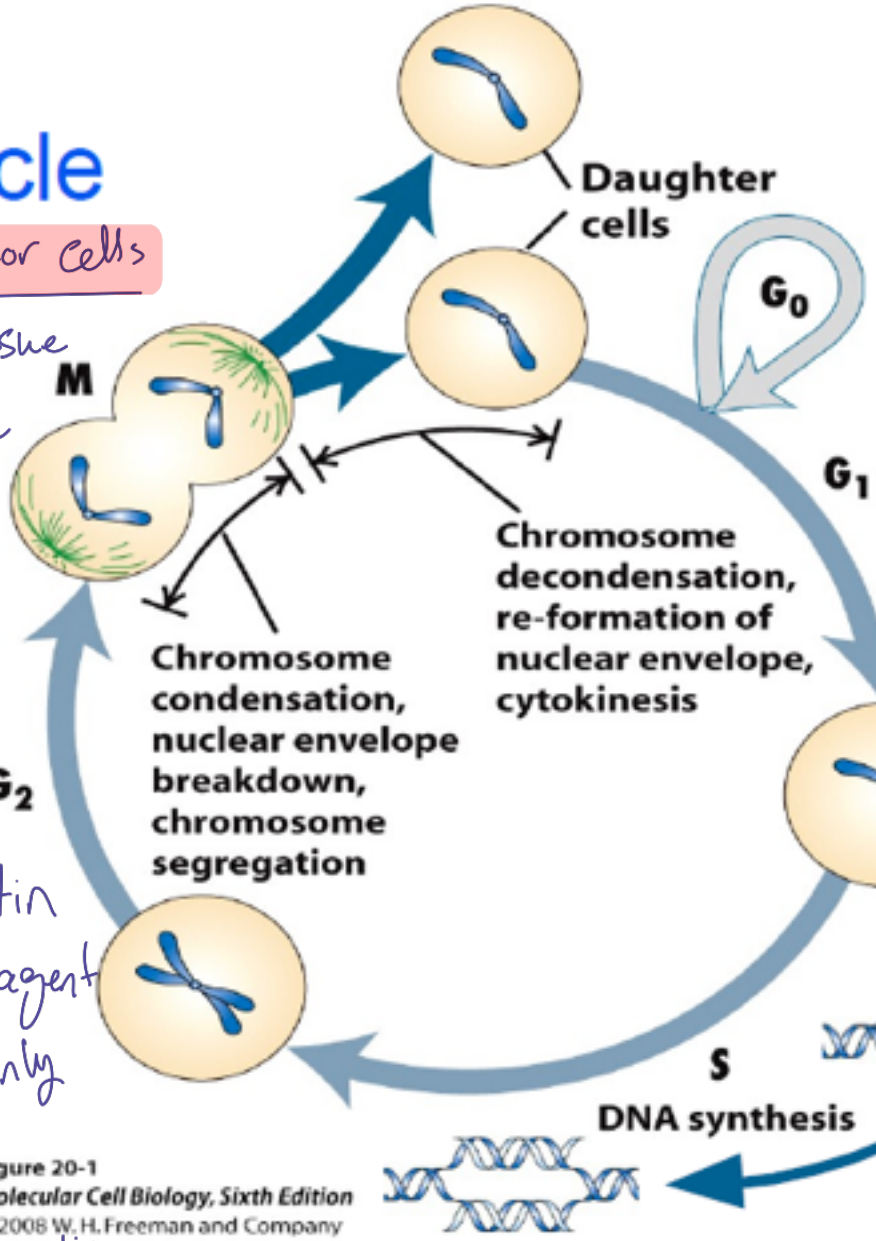


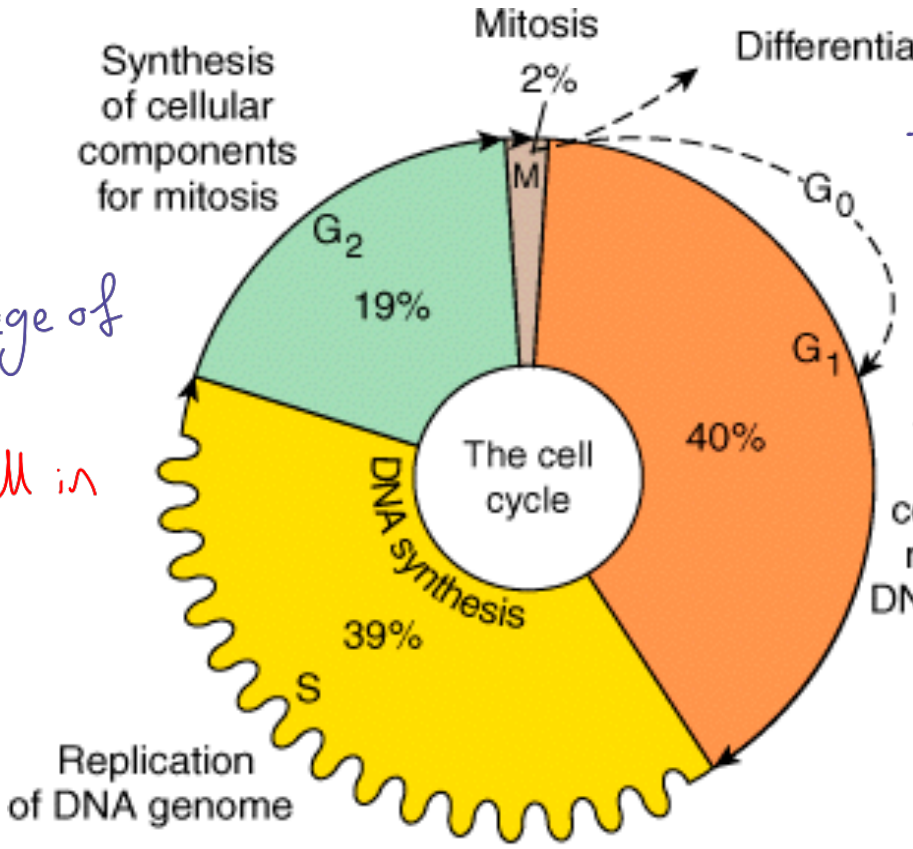
Figure 20-1
Molecular Cell Biology, Sixth Edition
© 2008 W. H. Freeman and Company

* So there are certin chemotheraputics agent that are effective only in Replicating cells
↓
Cells that are cycling

* on the other hand there are drugs that is cell cycle non-specific drugs. (CCNS drugs) which can sterlize the tumor cells wether they are cycling or restings → (in G0 phase)

& these drugs are said to be cell cycle speeific drugs (CCS drugs)

Cell cycle → Stages of cell divisions
→ Stages of preparing for cell divisions



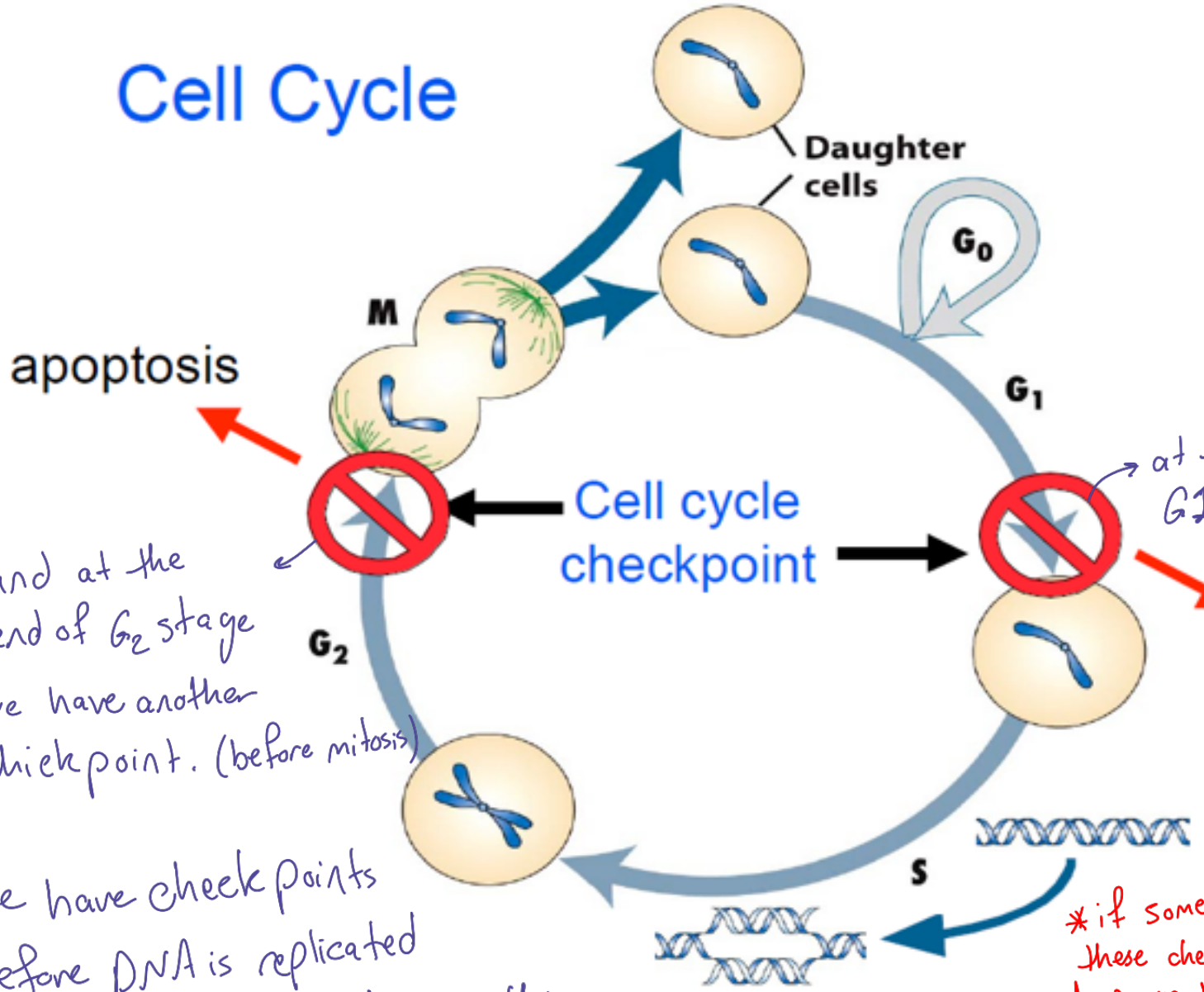
* the percentages refer to the avarage of time of each phase throw a malignent cell in the cycle

* the duration of G1 can vary markly

* Remember CCNS can kill G0 or cycling tumors
→ more sensitive

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Cell Cycle



at the end of G1 phase we have check point.

and at the end of G_2 stage we have another chiekpoint. (before mitosis)

* we have check points
So before DNA is replicated and the cell has relised something goes wrong, the cell will go in apoptosis (in normal cells)
↳ programmed cell death.

* if something goes wrong in these checkpoints, the cells will keep going throw the cell cycle even if we have mutation or wrong protein ⟹ cell transformed to malignent cell.

Chemotherapeutic Drugs: cell cycle dependence

Cell cycle specific: (CCS)

Antimetabolites
- Methotrexate
- Fluorouracil
- Capecitabine
- Cytarabine
- Mercaptopurine

Antibiotic
- Bleomycin

Agents from plants
- Vincristine, Vinorelbine
- Vinblastine
- Paclitaxel, Docetaxel
- Etoposide

Cell cycle nonspecific: (CCNS)

Alkylating agents
- Mechlorethamine
- Cyclophosphamide
- Chlorambucil
- Ifosfamide
- Carmustine
- Lomustine
- Busulfan

Platinum analogs
- Cisplatin, Carboplatin

Antibiotics
- Doxorubicin
- Epirubicin
- Dactinomycin

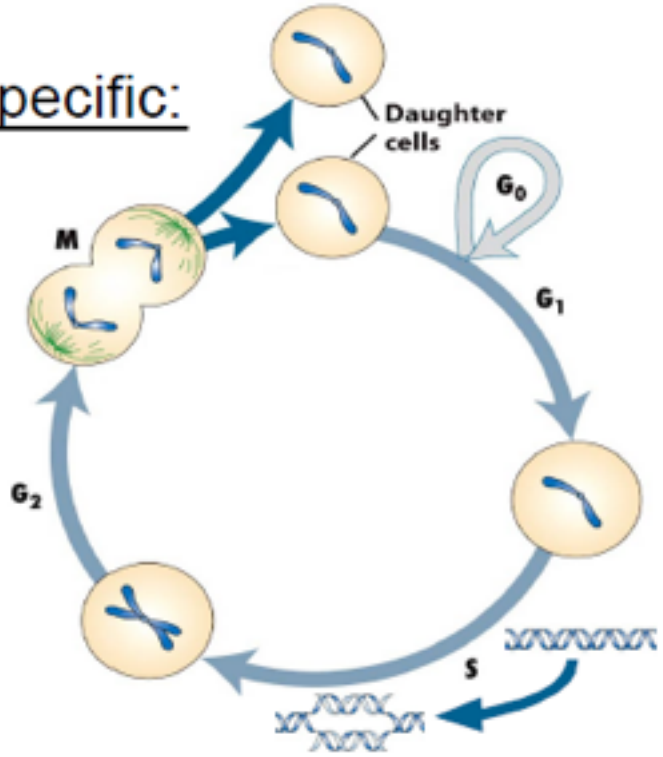
Chemotherapeutic Drugs:

Cell cycle phase specific action

M phase specific:

vincristine
vinblastine
vinorelbine
paclitaxel

→ plant derived drugs



S phase specific:

cytarabine
6-mercaptopurine
methotrexate

Alkylating Agents

↳ exeret their effect By covelantly binding neuclophilic groups on the vary cells constituents

Nitrogen Mustards

- Mechlorethamine
- Cyclophosphamide
- Chlorambucil
- Ifosfamide

Nitrosoureas

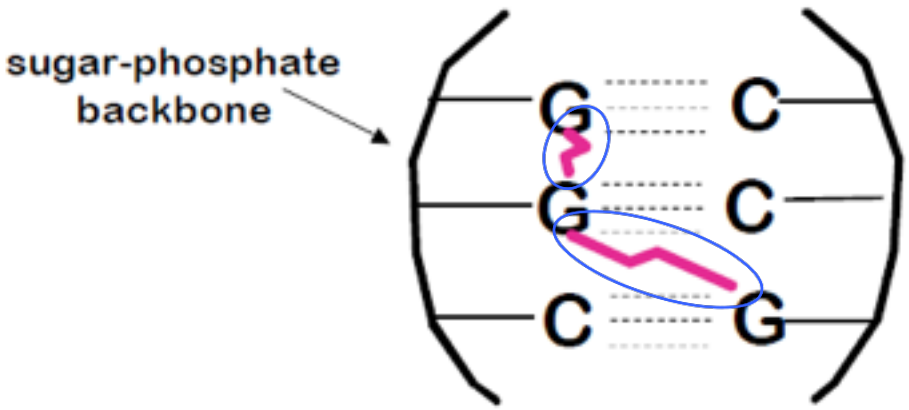
- Carmustine
- Lomustine

Alkyl sulfonate

- Busulfan

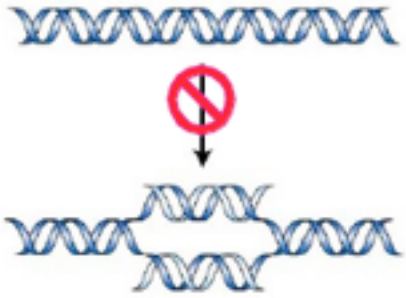
Platinum complexes

- Cisplatin
- Carboplatin



Crosslinked DNA

Interferes with DNA replication and causes cell cycle arrest



* Alkylation of DNA → prevent replication by prevent RNA translation & protein synthesis

Alkylating agents

- Mechanism of Action:
- Alkylation of DNA is the major interaction that leads to cell death.
- The major site of alkylation within DNA is the N7 position of guanine.
- These interactions can occur on a single strand, or both strands of DNA through cross-linking.

→ lead to interference with DNA replication ⇒ Cell cycle Arrest.

Other basis can interact but to less degree including N1, N3 in Adenosine, N3 of cytosine, O6 of guanine

* phosphate atoms or proteins associated with DNA can be affected by Alkylating agents.

→ Does not discriminate between cycling & Resting cells but mostly toxic for cycling one.

→ Used in general in lymphatic tumors + Solid cancer with other agents.

→ they are cytotoxic, mutogenic, carcinogenic → may cause leukemias.

Alkylating agents

Alkylation of guanine can result in:

- Miscoding through abnormal base-pairing with thymine.
- Depurination, by excision of guanine residues leading to DNA strand breakage.
- Cross-linking is of major importance to the cytotoxic action, and replicating cells are most susceptible. in the late G1 & S phases

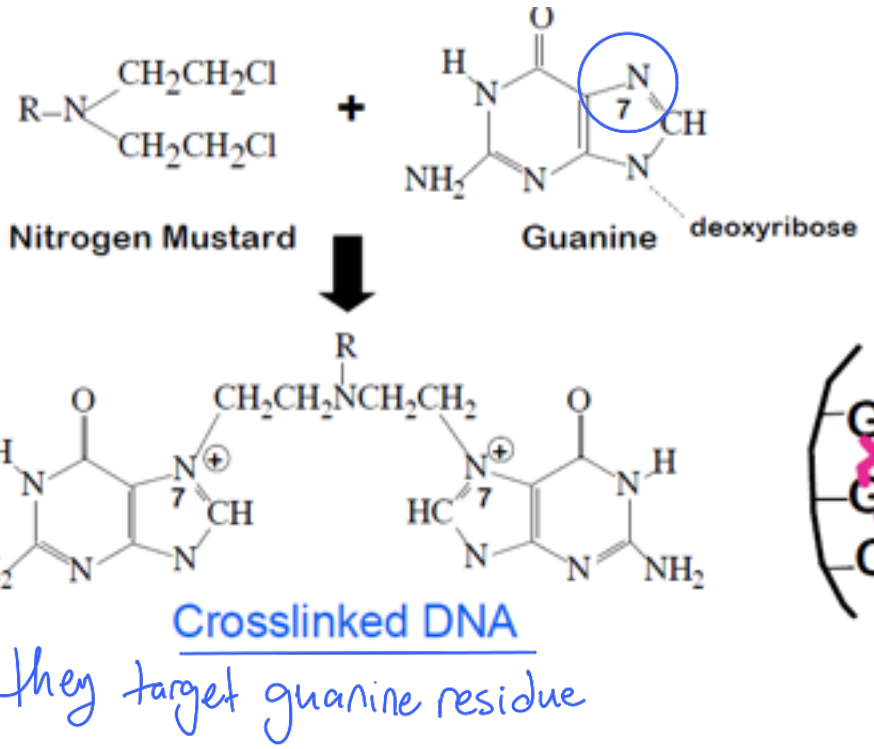
* Remember that the Alkylating agent affect replicating & resting cells.

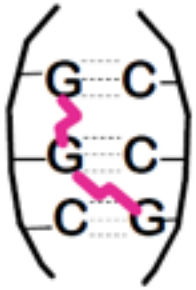
Alkylating Agents: Nitrogen Mustards

↳ of DNA → leads to cell death.

- Cyclophosphamide
- Ifosfamide
- Chlorambucil

* Major site of Alkylation is N7 position of guanine





* they target guanine residue

Cyclophosphamide

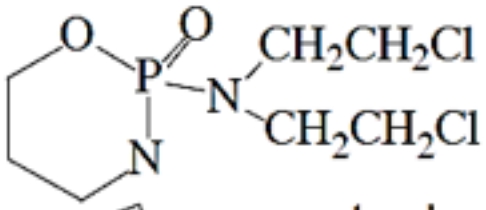
drug that need to be activited by metabolic steps.

Pharmacology:

- well absorbed orally. A prodrug which must be converted by liver cytochrome P450 to active metabolite

Toxicity:

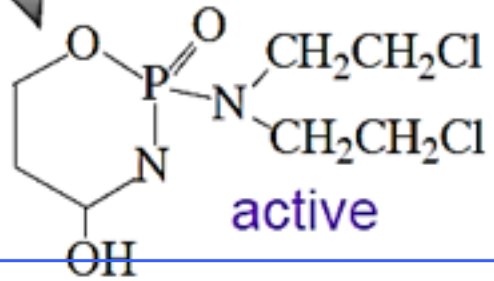
- N&V, cardiotoxicity, hemorrhagic cystitis, “bladder burn”, or hematuria - blood in urine, bone marrow toxicity



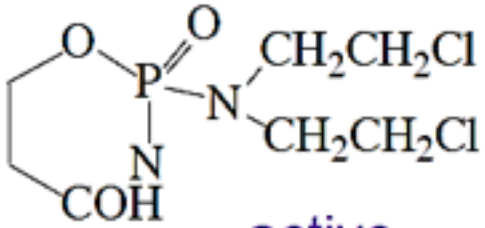
Cyclophosphamide inactive prodrug

cytochrome P450

two active metabolites



active



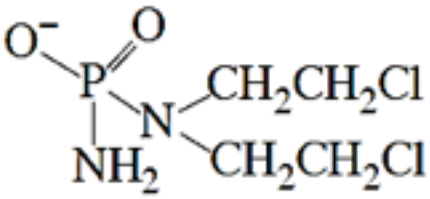
active

4-hydroxycyclophosphomide

Aldophosphomide

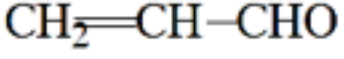
non-enzymatic step

By phosphatase



phosphoramide mustard:
toxic

+



MESNA

Detoxifing agent which prevents hemorrhagic cystitis in high dose of cyclophosphomide or other Alkylating agent called ifosfamide

acrolein:
toxic hemorrhagic cystitis, hematuria, "bladder burn"

* Aldophosphomide —Aldehyde oxidase, in the liver (detoxification)→ Carboxyphosphomide (inactive)

Ifosfamide (IFEX)

also is a prodrug that need to activated by Cytochrom P450. & some toxic metabolites can be produced.

- Activity greater than cyclophosphamide

Pharmacology:

- Given IV with MESNA (2-mercaptoethane
- sulfonate).
- Converted by liver cytochrome P450 to active & toxic metabolites.
- Toxicity: N&V, neurotoxicity (confusion), nephrotoxicity, hemorrhagic cystitis or hematuria (prevented by concurrent MESNA), cardiac toxicity with high dose, bone marrow toxicity

↳ to get rid of toxic metabolites that result from enzymatic & non-enzymatic conversion of isophosphamide into toxic metabolites which mentioned in last slides

↳ because it is Rapidly dividing.

* there are general toxicity of all Anticancer meds & there are some specific ones.

Alkylating agents: Nitrosoureas
Carmustine & Lomustine

↳ used to treat Blood dyscreasia
↳ act on N7 in guanine in DNA
↳ cytotoxic action because O6 in guanine ⇒ cross link between G&T in DNA.

Mechanism:

- inhibits DNA, RNA and protein synthesis

Pharmacology:

- lipid soluble (cross blood-brain barrier)

↳ So it can be used in Brain tumors & limited job on other cancer

Carmustine (BCNU)(1,3-bis (2-chloroethyl)-1-nitroso-urea): IV infusion over 1-2hrs

Lomustine (CCNU) (1-[2-chloroethyl]-3-cyclohexyl-1-chloroethylnitrosourea) : taken orally

* Excretion by Urinary excretion of the body.

Toxicity:

- profound delayed and cumulative bone marrow depression, N&V, pulmonary fibrosis, renal damage, reversible liver damage and leukemia.

* Streptozotocin is not used as chemotherapeutic agent but can belong to this family it is mainly toxic to β cells of pancerias ⟶ used to treat insulinomas but mainly used in Research perposes ⟶ in animals to get animal resemble T1DM in patient who can not do surgery ↵

Alkylating agents: Alkyl sulfonates Busulfan

- Pharmacology: well absorbed orally; plasma

half-life 2-3hrs

- Toxicity: N&V, bone marrow depression (stem

cells), pulmonary infiltrates and fibrosis.

major side effect.

*it is indecated in chronic myelogenous leukemia (CML)

TABLE 54–2 Alkylating agents and platinum analogs: Clinical activity and toxicities.

Alkylating Agent	Mechanism of Action	Clinical Applications	Acute Toxicity	Delayed Toxicity
Mechlorethamine	Forms DNA cross-links, resulting in inhibition of DNA synthesis and function	Hodgkin's and non-Hodgkin's lymphoma	Nausea and vomiting	Moderate depression of peripheral blood count; excessive doses produce severe bone marrow depression with leukopenia, thrombocytopenia, and bleeding; alopecia and hemorrhagic cystitis occasionally occur with cyclophosphamide; cystitis can be prevented with adequate hydration; busulfan is associated with skin pigmentation, pulmonary fibrosis, and adrenal insufficiency
Chlorambucil	Same as above	CLL and non-Hodgkin's lymphoma	Nausea and vomiting	
Cyclophosphamide	Same as above	Breast cancer, ovarian cancer, non-Hodgkin's lymphoma, CLL, soft tissue sarcoma, neuroblastoma, Wilms' tumor, rhabdomyosarcoma	Nausea and vomiting	
Bendamustine	Same as above	CLL and non-Hodgkin's lymphoma	Nausea and vomiting	
Melphalan	Same as above	Multiple myeloma, breast cancer, ovarian cancer	Nausea and vomiting	
Thiotepa	Same as above	Breast cancer, ovarian cancer, superficial bladder cancer	Nausea and vomiting	
Busulfan	Same as above	CML	Nausea and vomiting	
Carmustine	Same as above	Brain cancer, Hodgkin's and non-Hodgkin's lymphoma	Nausea and vomiting	Myelosuppression; rarely interstitial lung disease and interstitial nephritis
Lomustine	Same as above	Brain cancer	Nausea and vomiting	

important

important

non-hematopoetic cancers

Just in the box are required.

Can cross BBB

Nonclassic Alkylating Agents

used to treat → malignant melanoma, Hodgkin lymphoma, neuroblastoma, soft tissue sarcoma

Procarbazine (PO) and Dacarbazine (Parenteral)

PO → orally

for Hodgkin + Non-Hodgkin lymphoma + certain Brain tumors

Because they can pass BBB ⇑

- Inhibit DNA, RNA, and protein synthesis.
- Prolong interphase.
- Produce chromosome breaks, and DNA strand scission.
- Carcinogenic potential is higher than that of other alkylating agents.

* it can generate a metabolite by macrosomal enzyme called Azo procarbazine and result in H_2O_2 production
DNA strand breaking

* Another metabolites produced from procarbazine is weak mono amin oxidase inhibitors So when this drug is givin with other MOA inhibitor or tricyclic Antidepressant histamin, CNS depressent, Anti diabetic, Alcohol and amine containg food Can lead to toxicity from accomulation of these agent in addition to MOA inhibitor it will increase Catacholamines in the body.

Sammary: procarbazine ⟶ ↑ MOA inhibitor ⟶ ↑ Catacholamines

any drug that increase ↑ will lead to toxic increment in ↑

* Decarbazine need to be metabolised in the liver by oxidative demethylation to mono methyl dervative ⟹ will decompose to diazo methene which will generate methyl carbonium ion ▷ cytotoxic species associated with Decarbazine.

Nonclassic Alkylating Agents

Adverse effects:

- **Carcinogenesis- acute leukemia.** more than other of Alkylating agents.
- **Myelosuppression.**
- **Nausea and vomiting can be severe.**
- **Potent vesicants.** major side effect. tend to cause blistiring or extravasation → leakage of fluid out of place into surrounding area espicially the blood cells from vessels
- **CNS toxicity: neuropathy, ataxia, lethargy, and confusion.**

neuropathy → nerve damage → weakness & numbness & tingling

ataxia → uncoordination of the movement.

lethargy → lack of energy

Can lead to.

Altretamine	Same as above	Ovarian cancer	Nausea and vomiting	Myelosuppression, peripheral neuropathy, flu-like syndrome
Temozolomide	Methylates DNA and inhibits DNA synthesis and function	Brain cancer, melanoma	Nausea and vomiting, headache and fatigue	Myelosuppression, mild elevation in liver function tests, photosensitivity
Procarbazine	Methylates DNA and inhibits DNA synthesis and function	Hodgkin's and non-Hodgkin's lymphoma, brain tumors	Central nervous system depression	Myelosuppression, hypersensitivity reactions
Dacarbazine	Methylates DNA and inhibits DNA synthesis and function	Hodgkin's lymphoma, melanoma, soft tissue sarcoma	Nausea and vomiting	Myelosuppression, central nervous system toxicity with neuropathy, ataxia, lethargy, and confusion
Cisplatin	Forms intrastrand and interstrand DNA cross-links; binding to nuclear and cytoplasmic proteins	Non-small cell and small cell lung cancer, breast cancer, bladder cancer, cholangiocarcinoma, gastroesophageal cancer, head and neck cancer, ovarian cancer, germ cell cancer	Nausea and vomiting	Nephrotoxicity, peripheral sensory neuropathy, ototoxicity, nerve dysfunction
Carboplatin	Same as cisplatin	Non-small cell and small cell lung cancer, breast cancer, bladder cancer, head and neck cancer, ovarian cancer	Nausea and vomiting	Myelosuppression; rarely peripheral neuropathy, renal toxicity, hepatic dysfunction
Oxaliplatin	Same as cisplatin	Colorectal cancer, gastroesophageal cancer, pancreatic cancer	Nausea and vomiting, laryngopharyngeal dysesthesias	Myelosuppression, peripheral sensory neuropathy, diarrhea

CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia.

Antimetabolites

→ targets cancer cell metabolism that differ in with normal cells

are CCs drugs

Methotrexate (MTX):

- It is a folic acid analog that inhibits dihydrofolate reductase, interfering with the synthesis of tetrahydrofolate.
- THF serves as the key one-carbon carrier in the synthesis of thymidylate, purine nucleotides, and the amino acids serine and methionine.
- Thus, it interferes with the formation of DNA, RNA and key cellular proteins.

Antimetabolites

- Intracellular formation of polyglutamate metabolites, with the addition of up to 5-7 glutamate residues, is critically important for the therapeutic action of MTX.
- This process is catalyzed by folylpolyglutamate synthase.
- MTX polyglutamates are selectively retained within cancer cells.

Antimetabolites

Resistance develops due to:

1. **Decreased drug transport via the reduced folate carrier or folate receptor protein.**
2. **Decreased formation of cytotoxic MTX polyglutamate.**
3. **Increased levels of the target enzyme, dihydrofolate reductase, through gene amplification.**

Antimetabolites

4. Altered DHFR protein with altered affinity for MTX.
5. Activation of the multidrug resistance transporter P170 glycoprotein.

Antimetabolites

- MTX is administered by oral, intravenous, and intrathecal routes.
- Oral bioavailability is saturable and erratic at doses greater than 26 mg/m^2.
- Mainly eliminated by the kidney through glomerular filtration and active tubular secretion, thus dose reduction is needed in renal dysfunction.
- Its renal excretion is inhibited by aspirin, other NSAIDs, penicillins, and cephalosporins.

*So coadministration of these drugs with MTX cause toxicity.

Antimetabolites

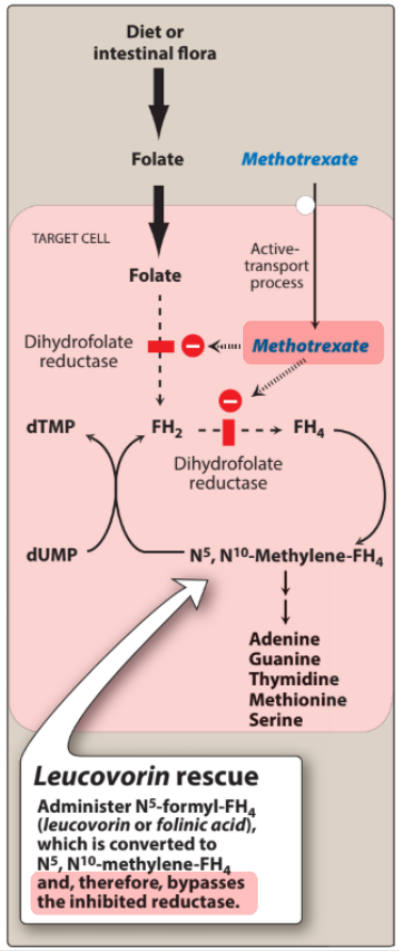
- The biologic effects of MTX can be reversed by administration of the reduced folate leucovorin (5-formyltetrahydrofolate).
- Leucovorin rescue is used in conjunction with high-dose MTX therapy to rescue normal cells from undue toxicity, and in accidental overdose.

Antimetabolites

Adverse effects:

- Mucositis, diarrhea
- Myelosuppression (neutropenia and thrombocytopenia).

* indication of MTX is
  - Breast cancer
  - Head & neck cancer
  - osteogenic sarcoma
  - CNS lymphoma
  - non-Hodgkin lymphoma
  - Bladder cancer
  - Chorio sarcoma



* MTX is used to treat other than cancer such as inflammatory condition of JIA, RA, psoriasis.

Antimetabolites

* natural ribose residue get replaced by D-arabinose so Ara-C act as pyramidine antagonist.

Cytarabine (Ara-C): is analoge of 2-deoxycytidine

- **It is an S phase specific antimetabolite that is converted by deoxycytidine kinase to the 5'-mononucleotide (ara-CMP).**
- **ara-CMP is further metabolized to the di- and tri-phosphate metabolites (ara-CTP).**
- **ara-CTP may be the main cytotoxic metabolite.**

* Ara-C is used in acute myelogenous leukemia in combination with → daunorubicin (Antibiotich)

6-thioguanine

Antimetabolites

- It competitively inhibits DNA polymerase-α and DNA polymerase-β, thereby blocking DNA synthesis and DNA repair, respectively.
- It is also incorporated into DNA (and RNA) which interferes with chain elongation and defective ligation of fragments of newly synthesized DNA.

Antimetabolites

* not effective orally because of de amination to non-cytotoxic arabinoside By cytidine deaminase in intestinal mucosa and the liver.

- **Given by IV infusion over 5-7 days.**

& Does not pentrate BBB

Adverse effects:

- **Myelosuppression (neutopenia and thrombocytopenia)**
- **Mucositis, nausea and vomiting**
- **Neurotoxicity (cerebellar ataxia).**

+ Hepatic dysfunction but rare

* Can be also given intrathecally → causing seizures and altered mental states. providing slow relase to CSF.

* Elimination by oxidative deamination to Ara-Uracil which is inactive & both Ara-C, Ara-Uracil is excreted in Urine.

TABLE 54–3 Antimetabolites: Clinical activity and toxicities.

Drug	Mechanism of Action	Clinical Applications	Toxicity
Capecitabine	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function	Breast cancer, colorectal cancer, gastroesophageal cancer, hepatocellular cancer, pancreatic cancer	Diarrhea, hand-foot syndrome, myelosuppression, nausea and vomiting
5-Fluorouracil	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function	Colorectal cancer, anal cancer, breast cancer, gastroesophageal cancer, head and neck cancer, hepatocellular cancer	Nausea, mucositis, diarrhea, bone marrow depression, neurotoxicity
Methotrexate	Inhibits DHFR; inhibits TS; inhibits de novo purine nucleotide synthesis	Breast cancer, head and neck cancer, osteogenic sarcoma, primary central nervous system lymphoma, non-Hodgkin's lymphoma, bladder cancer, choriocarcinoma → in the Uterus → required.	Mucositis, diarrhea, myelosuppression with neutropenia and thrombocytopenia
Pemetrexed	Inhibits TS, DHFR, and purine nucleotide synthesis	Mesothelioma, non-small cell lung cancer	Myelosuppression, skin rash, mucositis, diarrhea, fatigue, hand-foot syndrome
Cytarabine	Inhibits DNA chain elongation, DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of cytarabine triphosphate into DNA	AML, ALL, CML in blast crisis	Nausea and vomiting, myelosuppression with neutropenia and thrombocytopenia, cerebellar ataxia
Gemcitabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of gemcitabine triphosphate into DNA resulting in inhibition of DNA synthesis and function	Pancreatic cancer, bladder cancer, breast cancer, non-small cell lung cancer, ovarian cancer, non-Hodgkin's lymphoma, soft tissue sarcoma	Nausea, vomiting, diarrhea, myelosuppression
Fludarabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of fludarabine triphosphate into DNA; induction of apoptosis	Non-Hodgkin's lymphoma, CLL	Myelosuppression, immunosuppression, nausea and vomiting, fever, myalgias, arthralgias
Cladribine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of cladribine triphosphate into DNA; induction of apoptosis	Hairy cell leukemia, CLL, non-Hodgkin's lymphoma	Myelosuppression, nausea and vomiting, and immunosuppression
6-Mercaptopurine (6-MP)	Inhibits de novo purine nucleotide synthesis; incorporation of triphosphate into RNA; incorporation of triphosphate into DNA	AML	Myelosuppression, immunosuppression, and hepatotoxicity
6-Thioguanine	Same as 6-MP	ALL, AML	Same as 6-MP

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; DHFR, dihydrofolate reductase; dNTP, deoxyribonucleotide triphosphate; FdUTP, 5-fluorodeoxyuridine-5′-triphosphate; FUTP, 5-fluorouridine-5′-triphosphate; TS, thymidylate synthase.