Doctor.021
no. 5

HLS
PHARMACOLOGY

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Today we will focus on drugs used in treating cancer particularly drugs used in treating hematopoietic malignancies (leukemias &lymphomas)

Cancer Chemotherapy

Drugs for Leukemias and Lymphomas

Dr. Alia Shatanawi

Cancers are the 2nd leading cause for death &mortality after cardio vascular diseases

Cancer Chemotherapy

Magic bullet is a scientific term referred to a drug that can target cancer cells with specificity and selectivity without harming other normal cells. (Without side effects)

- "Magic bullet" drug, is a dream that did not materialize yet.
- 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

- Exploits the differences between normal and tumor cells. Further explanation next page
- Broad spectrum of activity. can kill many type of cancers
- Good distribution through the body. Can reach different parts of the body were cancer cells maybe present
- Non-immugenic.
- Adequate biological half life.
- Reasonably priced.

Studies are ongoing to discover treatments that act on targeting cancer cells without harming normal cells by emphasizing on differences between cancer and normal cells .

Currently , recent studies are developing cancer drugs that focus on inhibiting metabolic pathways occurring in cancer cells which is opposed to conventional cancer therapy “cytotoxic therapies”including chemo& radio therapy that kill cancer cells & lead to cell shrinkage quickly after getting the treatments

. New term has recently emerged which is targeted therapy that doesn’t immediately kill cancer cells rather it slows down cancer metabolism

So what do we mean by targeted therapy? We will talk about this term in the next lecture, which means drugs that target proteins responsible for cancer, cell, division, and growing and affect metabolic pathways in cancer cells in addition to inhibiting cancer cell glucose intake these drugs will affect the cancer cells for months after the treatment until the cells die

Cancer drugs have some disadvantages mentioned below

Current Anticancer Drugs

- Carcinogenic. Some cancer drugs, target, a certain type of cancer, but at the same time it can develop other type of cancer
- Mutagenic. Cause mutations
- Teratogenic. Pregnant women can't consume these drugs, because the upcoming fetus will develop teratogenicity
- Immunosuppressive.
- Very toxic, but tolerance can develop.

Cancer Chemotherapy - basics

Therapeutic index is the ratio between the dose that will cause toxicity and the dose that will give the effect needed so it indicates the drug safety

- Anticancer drugs have a small therapeutic index.
- They produce toxic side effects.
- Know the toxicities.

We have to remember these toxicities before prescribing drugs to try to choose as much as. possible the right choice that suits the patient

This is a way that helps in reducing 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.

Usually cancer cells are not detected until they're 1 g and each drug cycle kills 99.9٪ of cells, so 0.1 ٪cells aren't killed yet, and they have high potential to grow in a fast manner, so we have to repeat the drug cycle many times to make sure we killed all the cells

Cancer Chemotherapy - basics

Rapidly dividing cells are most susceptible -

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

Chemotherapy agents target the rapidly dividing cells which are cancer cells, bone marrow , hair follicles, and intestinal epithelium on the other hand, slow-growing tumors such as colon and lung cancers are less responsive

Slow growing tumors are less or unresponsive

- (colon and lung cancer)

Cell Cycle

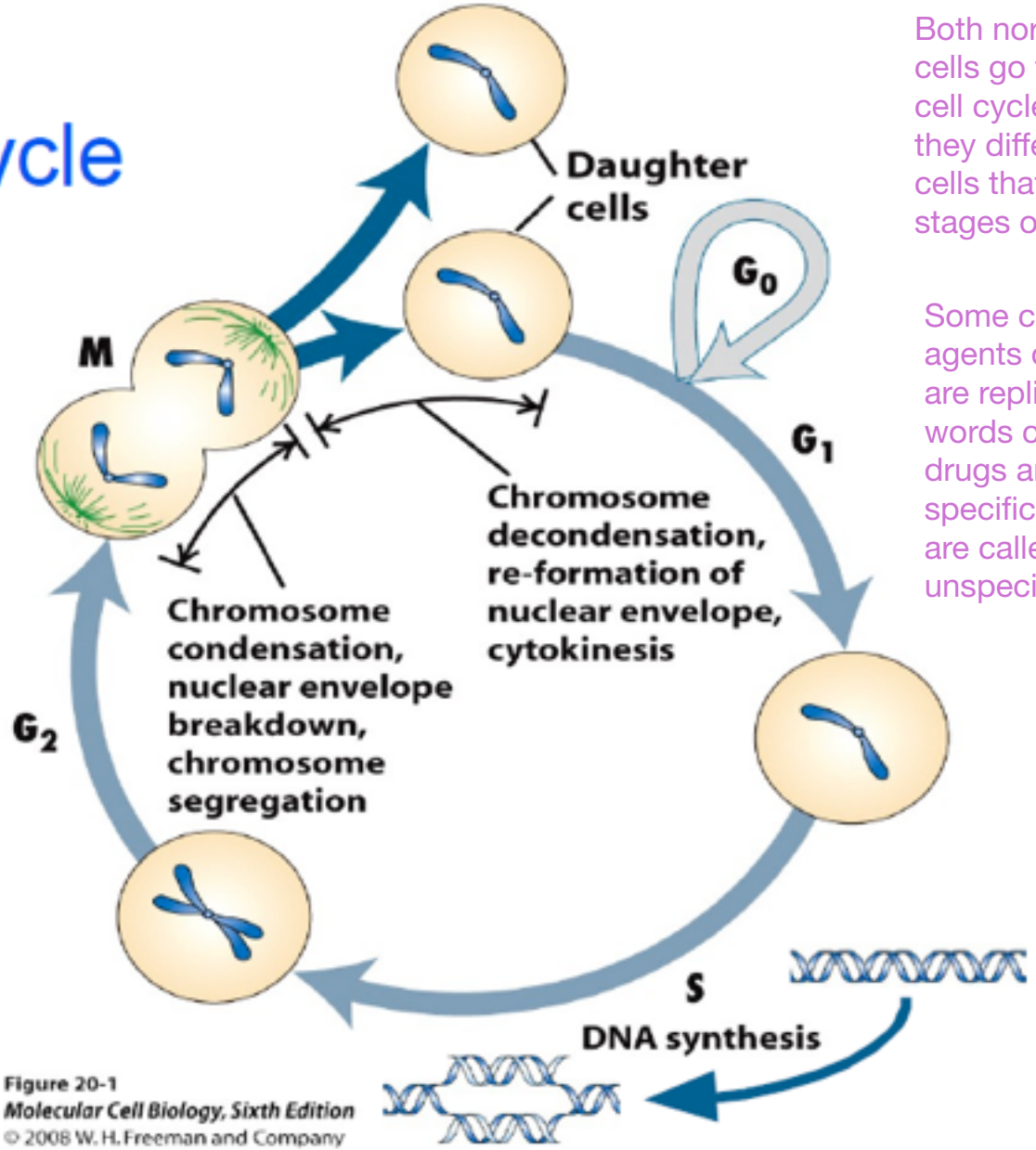


Figure 20-1
Molecular Cell Biology, Sixth Edition

Both normal and cancer cells go through the same cell cycle stages however, they differ in the number of cells that are on the various stages of the cycle.

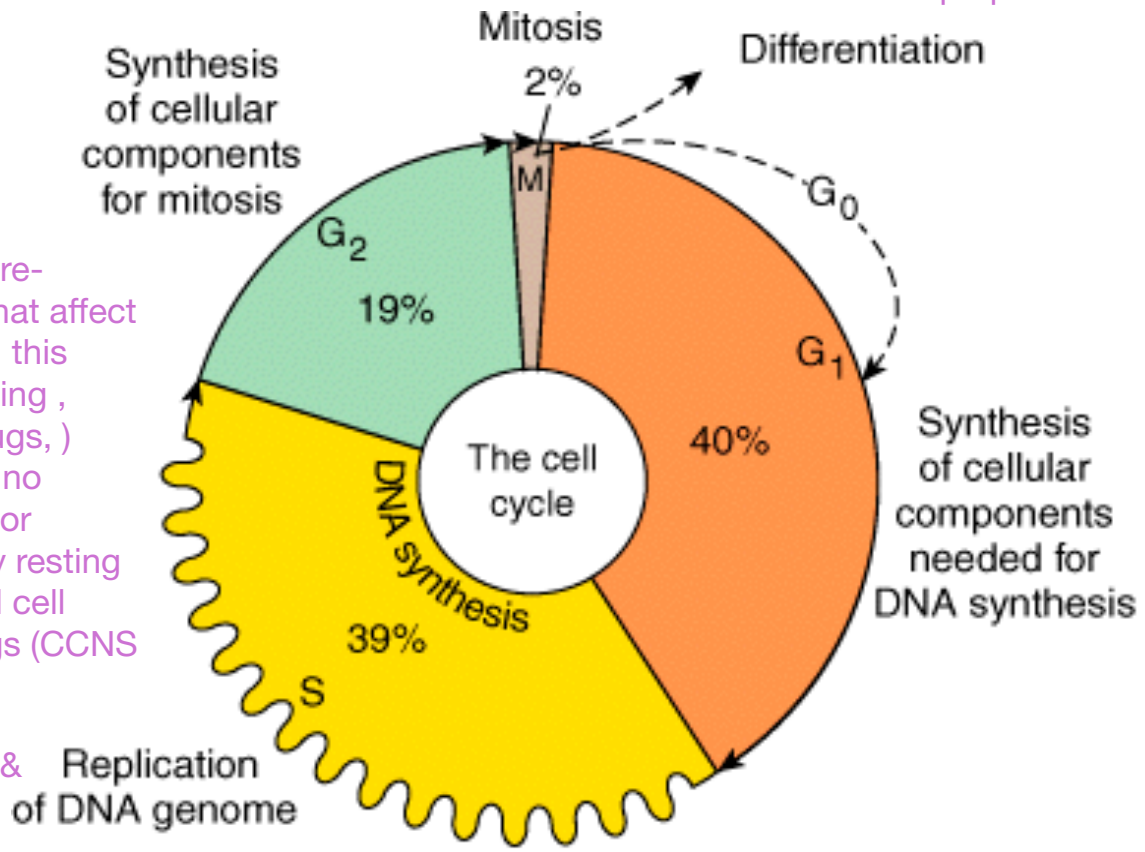
Some chemotherapy agents only target cells that are replicating “in other words cycling “, those drugs are called cell cycle specific drugs, other drugs, are called cell cycle unspecific drugs

The percentage presented in this graph shows the approximate time needed for a cancer cell to go through the cycle however, the duration of G1 phase can vary Markley

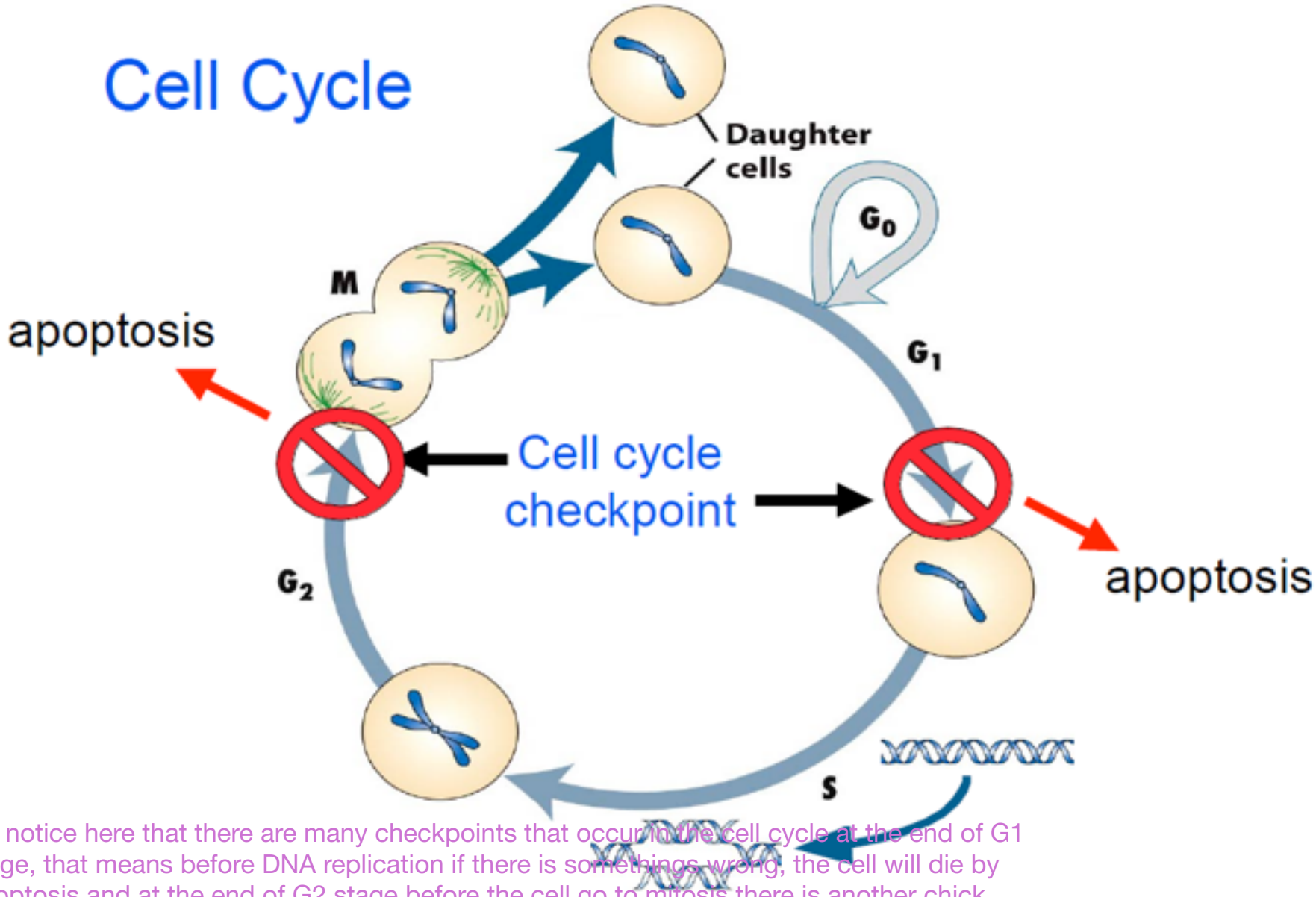
To re-emphasize this term, you should always remember that whether the cell is normal or not it goes through the same cell cycle including the stages of division, and stages of preparation to division

Another term should be re-emphasized the drugs that affect the cells that go through this cycle are called cell cycling , specific drugs,(CCS drugs,) other drugs, target cells no matter they are dividing or resting, and we mean by resting G0 phase and are called cell cycling nonspecific drugs (CCNS drugs)

Even though the cycling cells are more sensitive & responsive for CCNS



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



we notice here that there are many checkpoints that occur in the cell cycle at the end of G1 stage, that means before DNA replication if there is somethings wrong, the cell will die by apoptosis and at the end of G2 stage before the cell go to mitosis there is another chick point and again if there is something wrong, the cell will go apoptosis, which means cell programming death however, sometimes these checkpoints fail to figure out that the cell is abnormal and the cell continue the cycle, even though it has a mutation or wrong protein, etc. and this is when the cell turns to be malignant cell

Chemotherapeutic Drugs: cell cycle dependence

Cell cycle specific:

Antimetabolites
- Methotrexate
- Fluorouracil
- Capecitabine
- Cytarabine
- Mercaptopurine

Antibiotic
- Bleomycin

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

Cell cycle nonspecific:

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

Platinum analogs
- Cisplatin, Carboplatin

Antibiotics
- Doxorubicin
- Epirubicin
- Dactinomycin

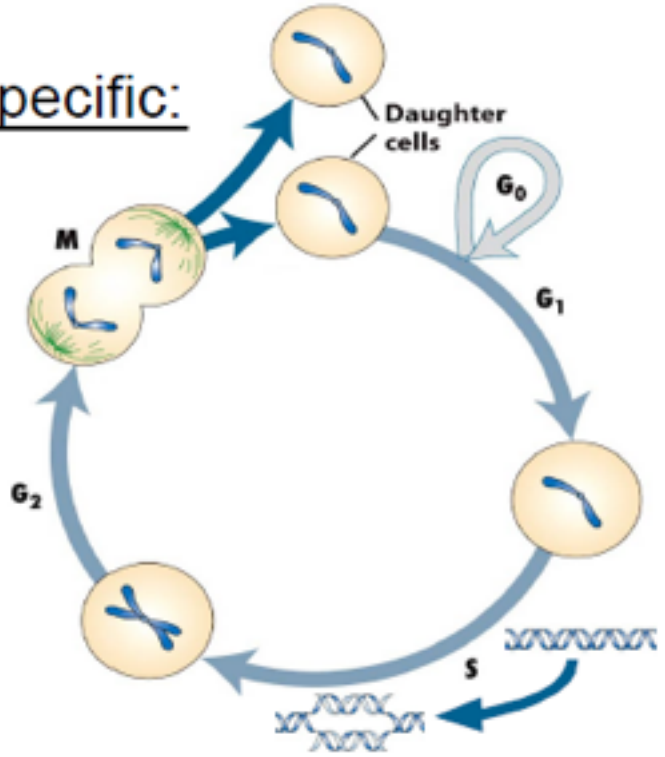
We will choose some drugs from each group that are related to blood malignancies and explain them farther

Chemotherapeutic Drugs:

Cell cycle phase specific action

M phase specific:

vincristine
vinblastine
vinorelbine
paclitaxel



S phase specific:

cytarabine
6-mercaptopurine
methotrexate

Alkylating Agents

Nitrogen Mustards

- Mechlorethamine
- Cyclophosphamide
- Chlorambucil
- Ifosfamide

Nitrosoureas

- Carmustine
- Lomustine

Alkyl sulfonate

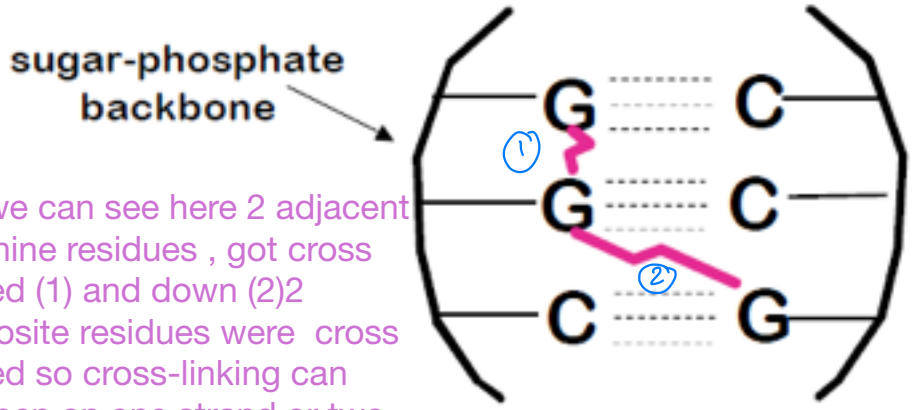
- Busulfan

Platinum complexes

- Cisplatin
- Carboplatin

Neocluphilic … have the tendency to donate electron
Alkylating …adding alkyl group

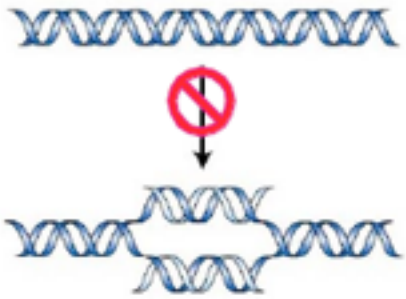
Alkylating agents produce their toxic effect by covalently bonding to different neocluphilic groups of different cell contents as an example, some drugs, alkylate the DNA and definitely it will stop cell replication and lead to cell arrest however alkylating agents don't discriminate between cancer cells and normal cells but usually rapidly replicating cells are more sensitive than other cells. These agents are used for lymphatic tumors in addition to solid cancers with combination with other agents .
These drugs are mutagenic and carcinogenic &can lead to second malignancies, such as leukemias



As we can see here 2 adjacent guanine residues , got cross linked (1) and down (2)2 opposite residues were cross linked so cross-linking can happen on one strand or two different strands of DNA

Crosslinked DNA

Interferes with DNA replication and causes cell cycle arrest



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.

By inhibiting DNA replication mRNA translation will be inhibited And so the protein synthesis

Other position can interact with the alkylation drugs, such asN1and N3 in adenine N3 in cytosine and O6 in guanine , the phosphate atom, and some proteins, but to a lesser degree

As mentioned in the previous slide .

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.

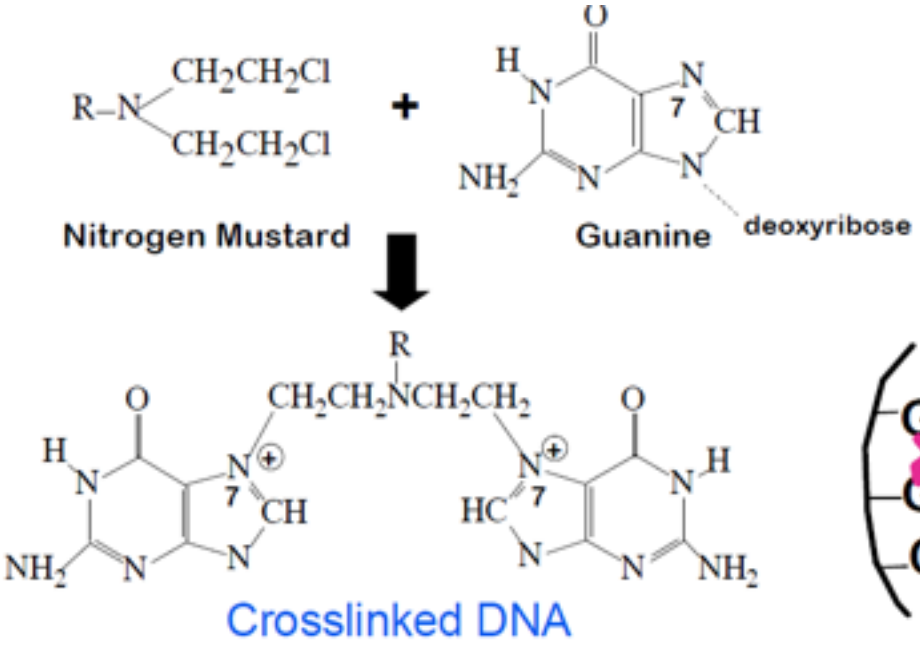
These agents are not cell cycling specific, but cells at the late G1 phase &on the S phase are more susceptible

Alkylating Agents: Nitrogen Mustards

These three drugs have the same mechanism of action

- Cyclophosphamide
- Ifosfamide
- Chlorambucil

As we can see here in the figure the these drugs, cross-link, the DNA and mainly they affect N7 position of guanine residue



Cyclophosphamide

Pharmacology:

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

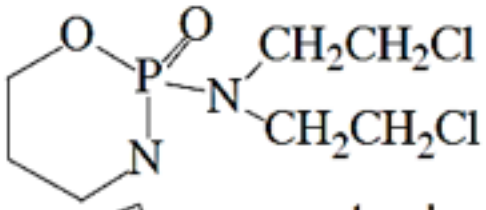
A

Toxicity:

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

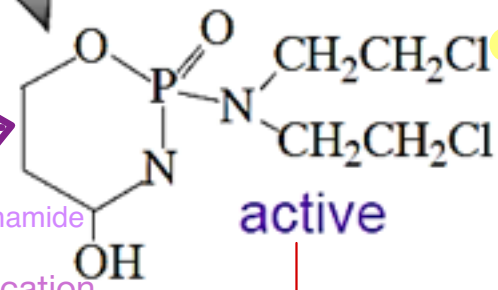
Look !

* بعرف انه هي الصفحة محجّة
رتبت التفاعلات حسب ترتيب
شرح الدكتورة بالسلايد إلي بعد
يا رب تستفيدوا

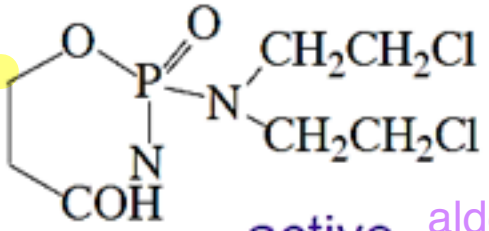


Cyclophosphamide inactive prodrug

cytochrome P450 Or microsomal enzyme, In the liver



equilibrium



active

active

4-hydroxycyclophosphamide

Detoxification

4-Ketocyclophosphamide
In active

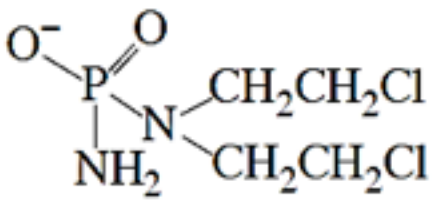
Phosphatase

aldophosphamide

Aldehyde oxidase enzyme

Detoxification

carboxyphosphamide
In active



+

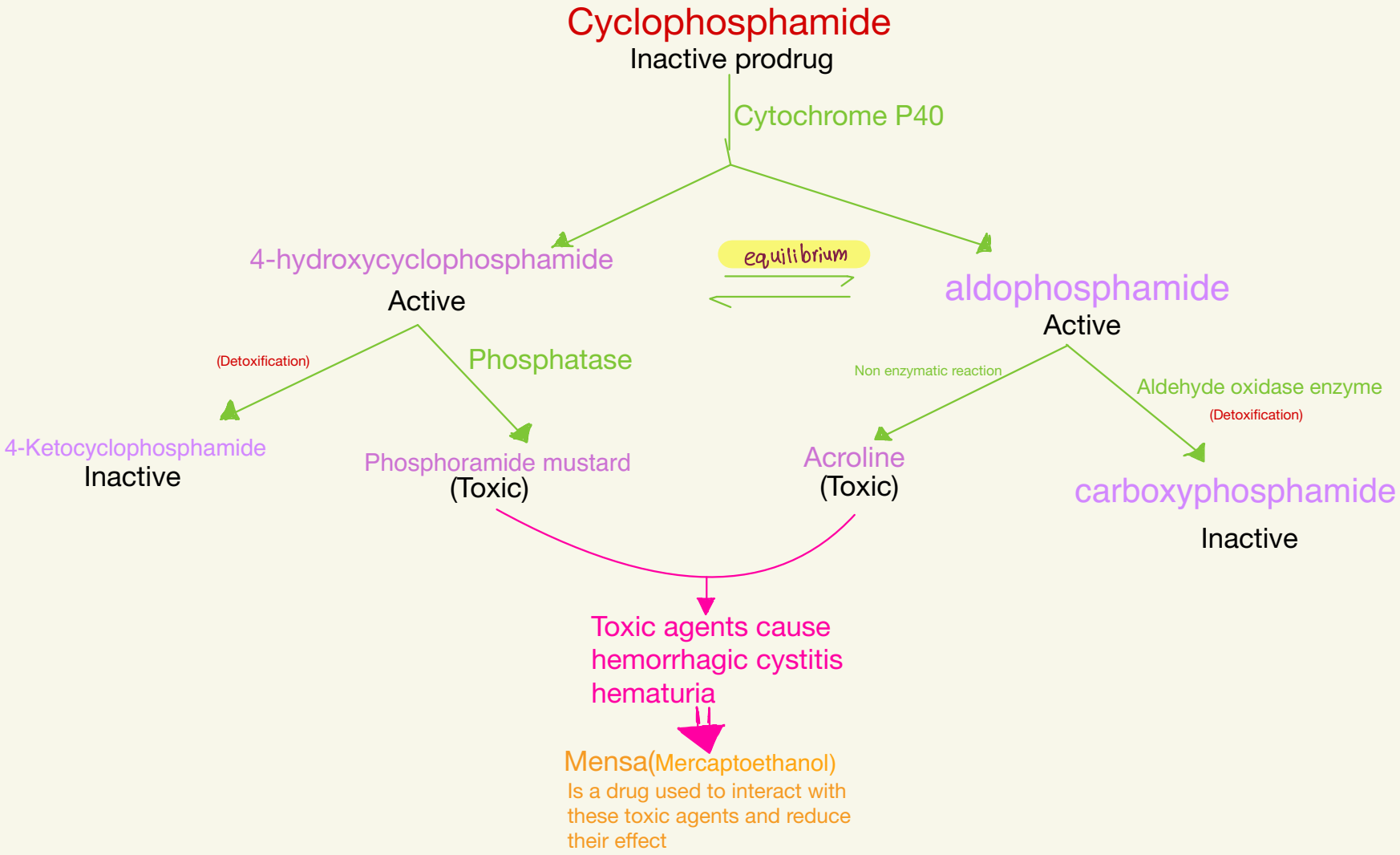
$CH_2{=}CH{-}CHO$

MESNA
(Mercaptoethane sulfonate)

Is a drug used to interact with these toxic agents and reduce their effect

phosphoramide mustard:
toxic

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


Cyclophosphamide
Inactive prodrug
Cytochrome P40
4-hydroxycyclophosphamide
Active
equilibrium
aldophosphamide
Active
(Detoxification)
Phosphatase
Non enzymatic reaction
Aldehyde oxidase enzyme
(Detoxification)
4-Ketocyclophosphamide
Inactive
Phosphoramide mustard
(Toxic)
Acroline
(Toxic)
carboxyphosphamide
Inactive
Toxic agents cause
hemorrhagic cystitis
hematuria
Mensa(Mercaptoethanol)
Is a drug used to interact with
these toxic agents and reduce
their effect

Ifosfamide (IFEX)

Alkylating agent
It goes the same previous Pathway

- Activity greater than cyclophosphamide

Pharmacology:

- Given IV with MESNA (2-mercaptoethane
- sulfonate).

The purpose of adding MESNA is to reduce the toxic effect by the enzymatic and non-enzymatic reactions which convert the drug to toxic metabolites

- 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

Nausea ← → Vomiting

Remember that there are common nonspecific toxic effects for cancer drugs, and some other specific toxic effect. The doctor mentioned that she wants us to emphasize on the specific toxic effects

Alkylating agents: Nitrosoureas Carmustine & Lomustine

Streptozotocin is a drug that is not used in treating cancer, but belong to this family it's toxic to beta cells of islet Langerhans of the pancreas it's usually used For research purposes to produce animals with type one diabetes although this drug was used for treating some insulinomas but this use is limited now

Mechanism:

- inhibits DNA, RNA and protein synthesis

Pharmacology:

- lipid soluble (cross blood-brain barrier)

As a result can be used in some brain tumors and they have limited use in other type of cancers

Carmustine (BCNU) : IV infusion over 1-2hrs

Lomustine (CCNU) : taken orally

Toxicity:

They act on N7 position in guanine however, the toxic effects are produced by acting on o7 guanine which lead to cross linking between guanine and cytosine. They are eliminated by urinary excretion

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

Alkylating agents: Alkyl sulfonates

Busulfan

This drug is indicated in chronic myelogenous leukemia

- Pharmacology: well absorbed orally; plasma

half-life 2-3hrs

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

cells), pulmonary infiltrates and fibrosis.

Nonclassic Alkylating Agents

Orally active

Used for Hodgkin's and non-Hodgkin's lymphoma , as well as brain tumors because it can pass blood brain barrier

Parentral

Used to treat malignant melanoma ,Hodgkin lymphoma ,certain soft tissue sarcomas ,and neuroblastoma

Procarbazine (PO) and Dacarbazine (Parenteral)

It has to be converted to an active form by oxidative demethylation to a monomythel derivative which will compose to azomethine and generate mythel carbonium ion which is believed that it is the cytotoxic ion associated with the drug

- 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 produce by microsomal enzymes metabolite called azo procarbazine responsible for the formation of hydrogen peroxide, hydrogen peroxide could be the responsible for the DNA strand scission (procarbazine)

Another metabolite produced by this drug monoamine oxidase inhibitor, so when this drug is used with another monoamine oxidase inhibitor ,sympatho mimic agents (tricyclic antidepressant),alcohol,antidiabetic agents, , antihistamine and central nervous system anti depressant can lead to toxicity from accumulation of catecholamines in the body .

Nonclassic Alkylating Agents

Adverse effects:

- Carcinogenesis- acute leukemia.
- Myelosuppression.
- Nausea and vomiting can be severe.
- Potent vesicants.
- CNS toxicity: neuropathy, ataxia, lethargy, and confusion.

it has the potential to cause tissue damage through blistering and ulceration it can also cause Extravasation: the unintentional leakage of vesicant fluids and blood cells from the vein into the surrounding tissue.

Lack of energy
خمول

Which leads to nerve damage resulting in weakness and numbness

Uncoordination of the movement

Antimetabolites

Cell cycle specific agents

Although all the differences between normal and cancer cells are not yet discovered, but still, we have some differences that makes cancer cells more responsive, and sensitive to antimetabolites

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.

So this gives the specifity to 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 co- administration of these drugs, with methotrexate can lead to accumulation of methotrexate and exceeds its toxic effects

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).

The clinical indications for using methotrexate are breast, cancer, head, and neck, cancer, non Hodgkin lymphoma ، osteogenic sarcoma , primary central nervous system lymphoma , chorio carcinoma,bladder cancer , It's also used to treat conditions other than cancer, such as inflammatory condition of juvenile idiopathic arthritis. rheumatoid arthritis. And also psoriasis.

Antimetabolites

Cytosine arabinoside

Cytarabine (Ara-C): Analog of two 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.

The natural ribose residues get replaced by dearabinose so it acts as pyrimidine antagonist

It's used in Acute myeloid leukemia in combination with two other drugs which are 6-Thioguanine witches, another antimetabolite in addition to antibiotic called Daunorubicin

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

It's not effective when given orally because of it, diamination into noncytotoxic, uracil arabinoside by an enzyme called cytidine deaminase in the intestinal mucosa and liver

- Given by IV infusion over 5-7 days.

Adverse effects:

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

Intrathecal injection of this drug Can cause seziures and altar mental state

- They can also produce hepatic dysfunction, but occasionally not with every patient

It is distributed all over the body, but it can't penetrate to the central nervous system, insufficient amount, so it's not used in meningeal leukemia however, for the treatment of this condition, it can be injected intrathecally. Which is a new preparation that provides slow-release into the cerebral spinal fluid

ARC goes extensive deamination in the body to uracil arabinoside which is pharmacologically inactive metabolite and both of these excreted in urine