Cancer Chemotherapy

Drugs for Leukemias and Lymphomas

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Cancer Chemotherapy

- "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.
- Broad spectrum of activity.
- Good distribution through the body.
- Non-immugenic.
- Adequate biological half life.
- Reasonably priced.

Current Anticancer Drugs

- Carcinogenic.
- Mutagenic.
- Teratogenic.
- Immunosuppressive.
- Very toxic, but tolerance can develop.

Cancer Chemotherapy - basics

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

Cancer Chemotherapy - basics

Rapidly dividing cells are most susceptible -

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

Slow growing tumors are less or unresponsive

- (colon and lung cancer)

Cell Cycle

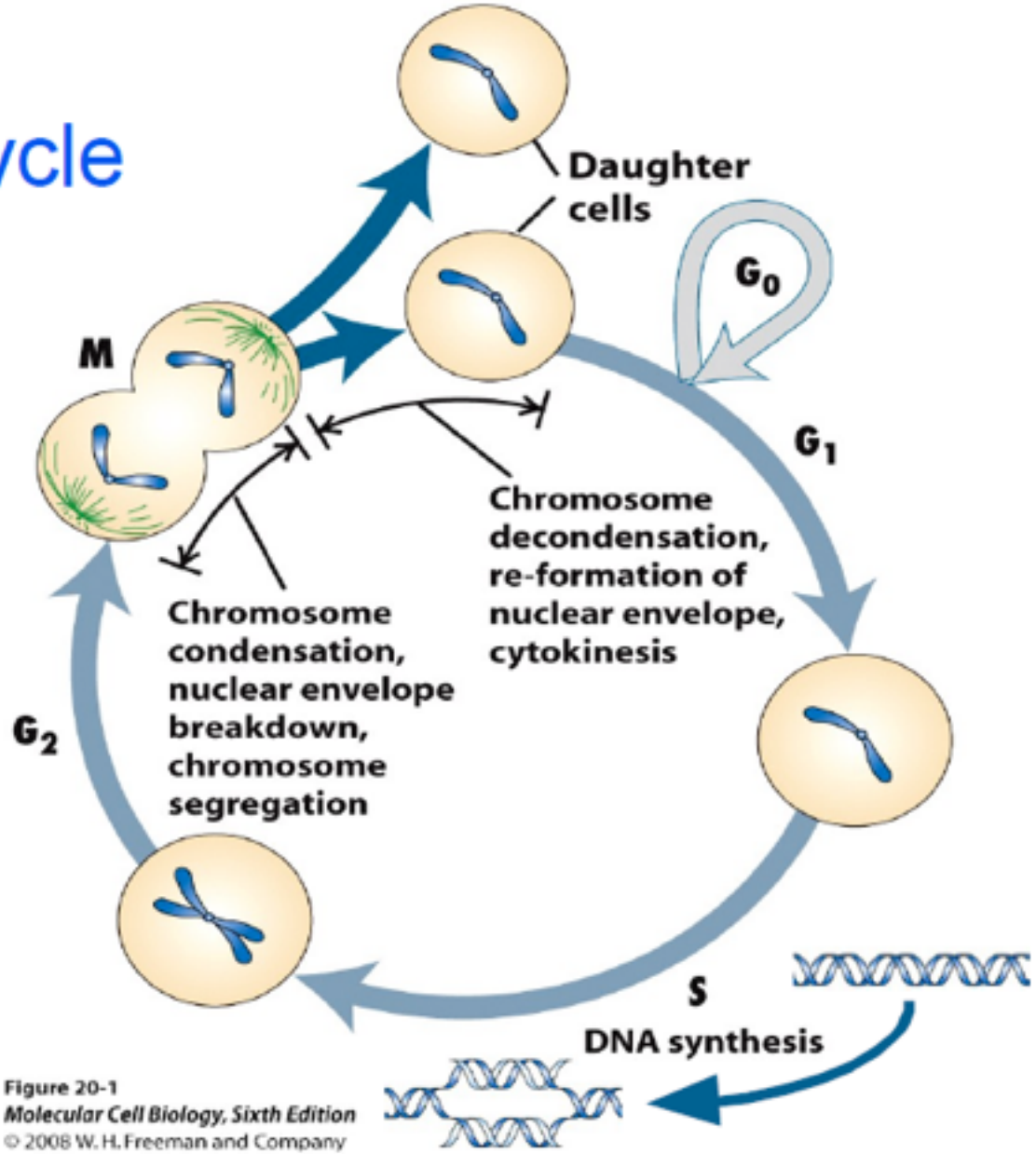
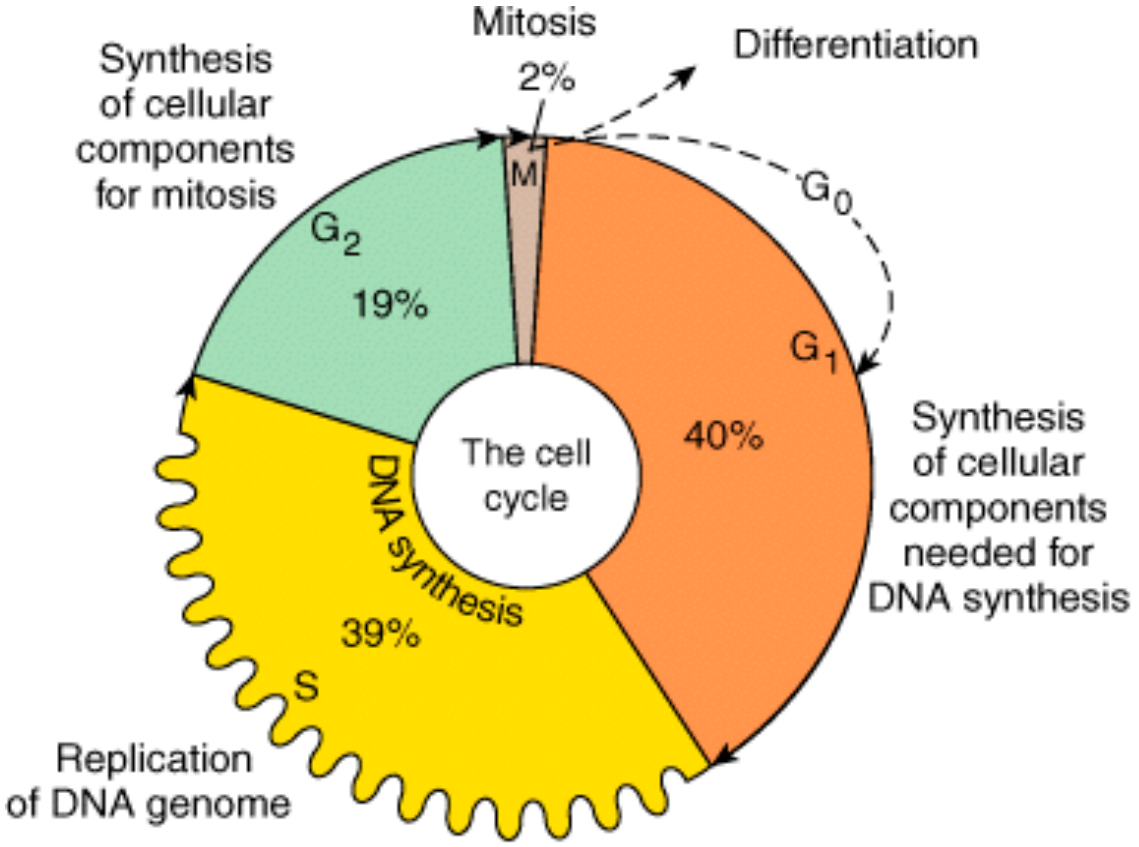
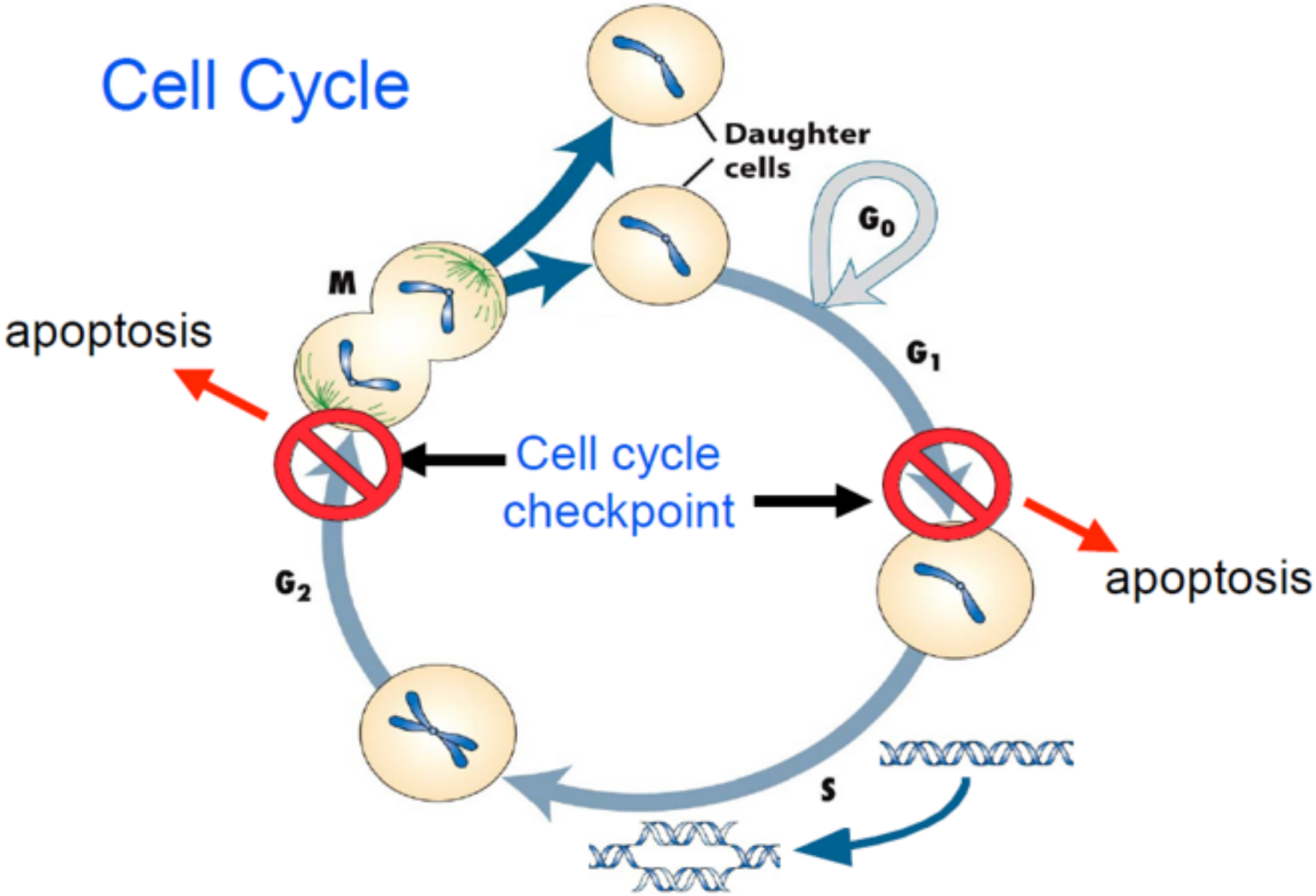


Figure 20-1
Molecular Cell Biology, Sixth Edition



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

Cell Cycle


Daughter cells
G_0
M
apoptosis
G_1
Cell cycle checkpoint
apoptosis
G_2
S

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

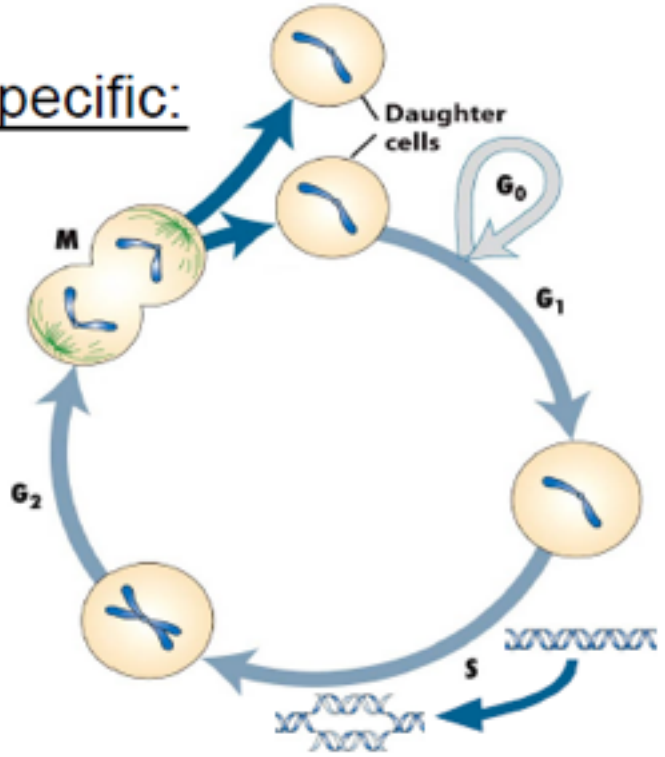
Antibiotics
- Doxorubicin
- Epirubicin
- Dactinomycin

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

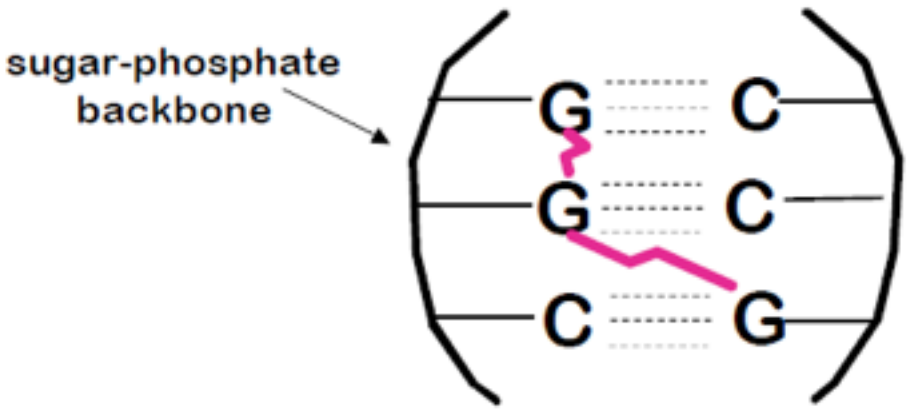
- Carmustine
- Lomustine

Alkyl sulfonate

- Busulfan

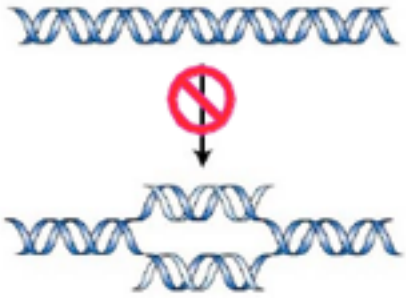
Platinum complexes

- Cisplatin
- Carboplatin



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.

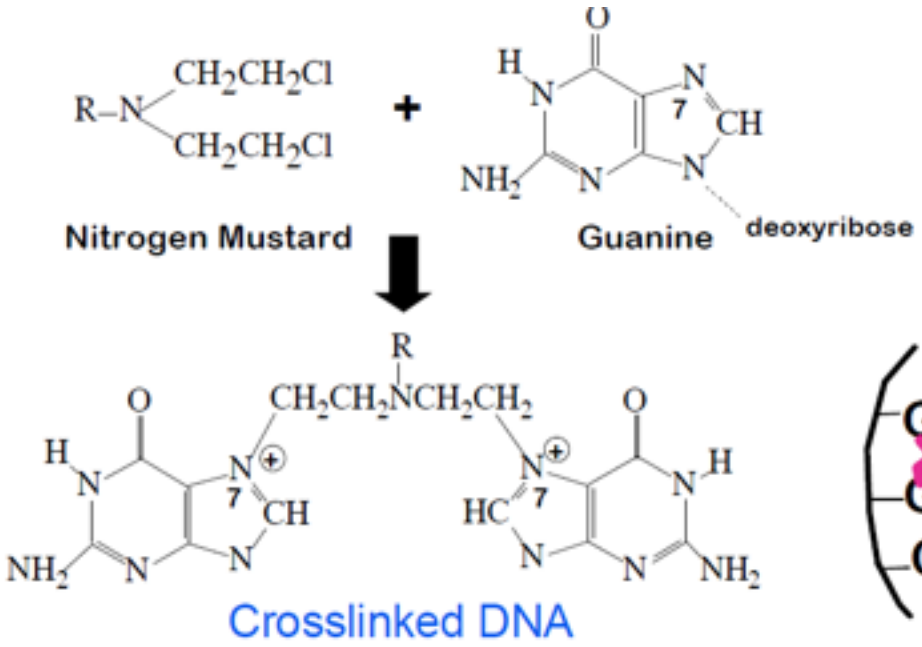
Alkylating agents

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.

Alkylating Agents: Nitrogen Mustards

- Cyclophosphamide
- Ifosfamide
- Chlorambucil



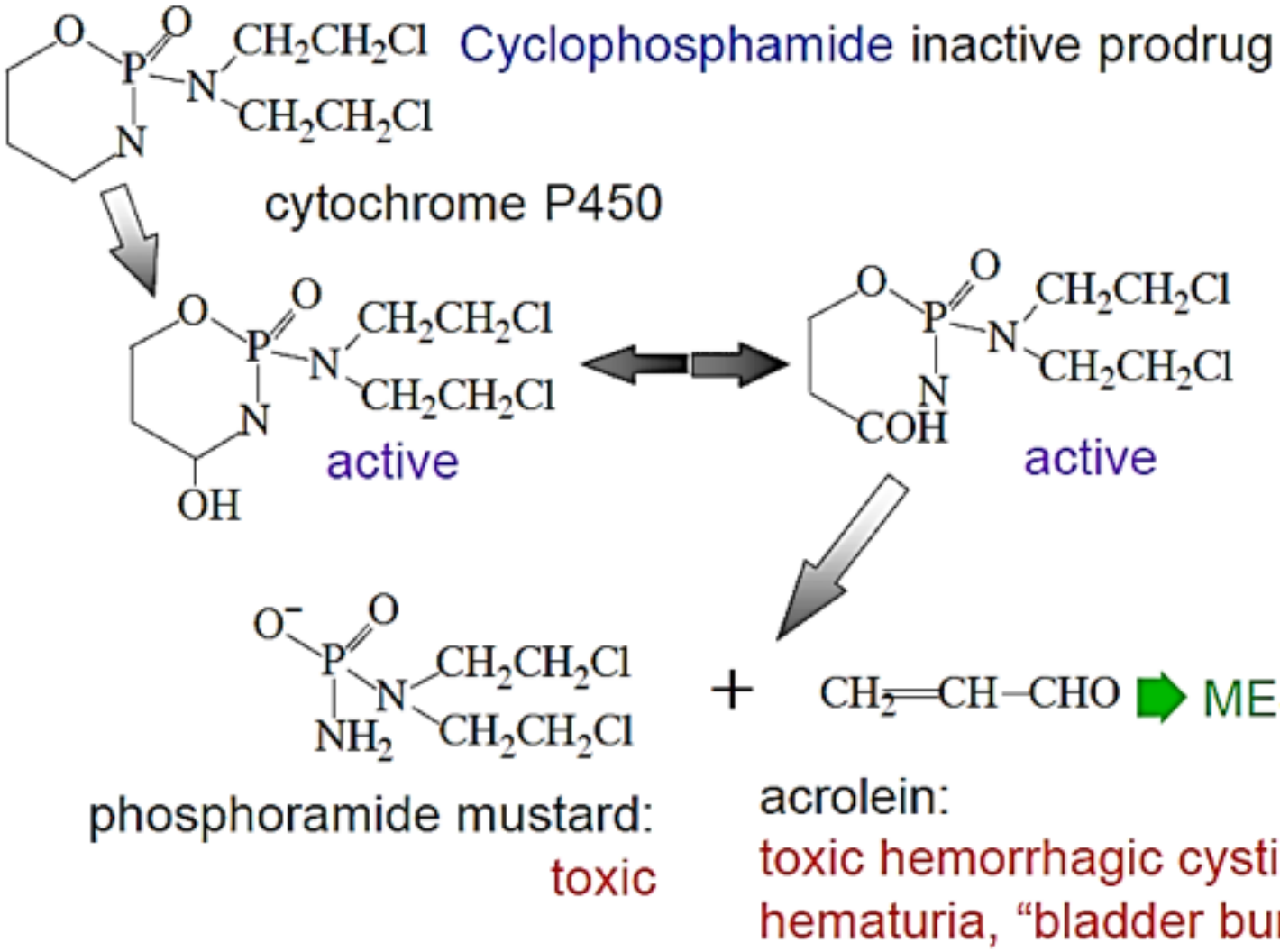
Cyclophosphamide

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
active
active
phosphoramide mustard:
toxic
acrolein:
toxic hemorrhagic cystitis,
hematuria, "bladder burn"
MESNA

Ifosfamide (IFEX)

- 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

Alkylating agents: Nitrosoureas Carmustine & Lomustine

Mechanism:

- inhibits DNA, RNA and protein synthesis

Pharmacology:

- lipid soluble (cross blood-brain barrier)

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

Lomustine (CCNU) : taken orally

Toxicity:

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

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.

Nonclassic Alkylating Agents

Procarbazine (PO) and Dacarbazine (Parenteral)

- 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.

Nonclassic Alkylating Agents

Adverse effects:

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

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.

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.

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).**

Antimetabolites

Cytarabine (Ara-C):

- 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.

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

- Given by IV infusion over 5-7 days.

Adverse effects:

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