بسم الله الرحمن الرحيم

Anticancer drugs (part 1)

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INTRODUCTION

❑Benign tumors (where cell growth is increased, but the cells do not invade nearby tissue or spread all over the body) is not cancer.

❑ Malignant tumors (cancer); the cells divide out of control and invade nearby healthy tissue. Cancer cells can spread (metastasize) through blood stream and lymphatic system.

❑**Characters of Cancer cells:**

1. Rapid **proliferation** (fast mitosis without apoptosis)
2. **Avoidance of apoptosis** (no programmed cell death)
3. **Loss of contact growth inhibition**
4. **Immortalization**
5. **Abnormal differentiation**
6. Induction of **angiogenesis**

Adjuvant anticancer chemotherapy

Anticancer Chemotherapy (including cytotoxic drugs) is a basic line of treatment after Surgery, Radiation and immunotherapy.

Anticancer drugs aim at decreasing residual cancer cells & metastases to achieve:

1- Cure or prolonged 'remission': all macroscopic & microscopic features of the cancer disappear, though disease may persist or relapse

Examples: in children (Acute Lymphoblastic Leukaemia, Wilm`s tumor, Ewing`s sarcoma), in adults (Hodgkin's lymphoma, some leukemia, testicular teratoma and choriocarcinoma).

2. Palliation: ↓ tumor size , ↓ symptoms & improve quality of life.

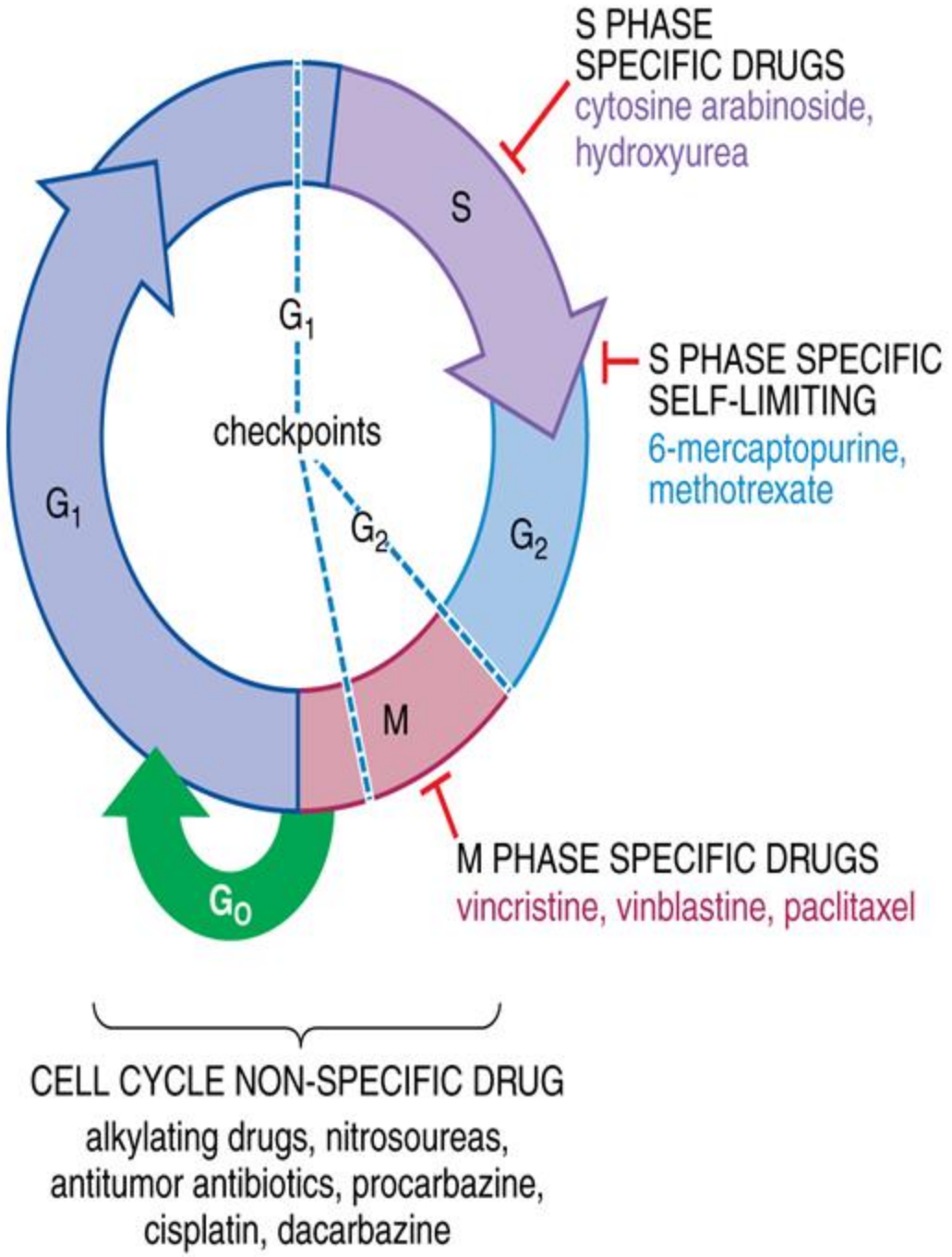
Examples: Breast cancer, ovarian cancer, endometrial carcinoma, cancer of lung and Non-Hodgekin lymphoma.

Classification of anticancer drugs

Cell-Cycle Specificity

Drugs that act specifically on phases of the cell cycle are called **cell cycle specific (CCS)** and are more effective in tumors with high-growth fraction (leukemias, lymphomas).

Drugs that are **cell-cycle nonspecific** (many bind to and damage DNA) can be used in tumors with low-growth fraction, as well as tumors with high-growth fraction.



Cytotoxic drugs

Log-Kill Hypothesis

Cytotoxic actions of anticancer drugs follow first-order kinetics: They kill a fixed percentage of tumor cells, not a fixed number, which is one rationale for drug combinations.

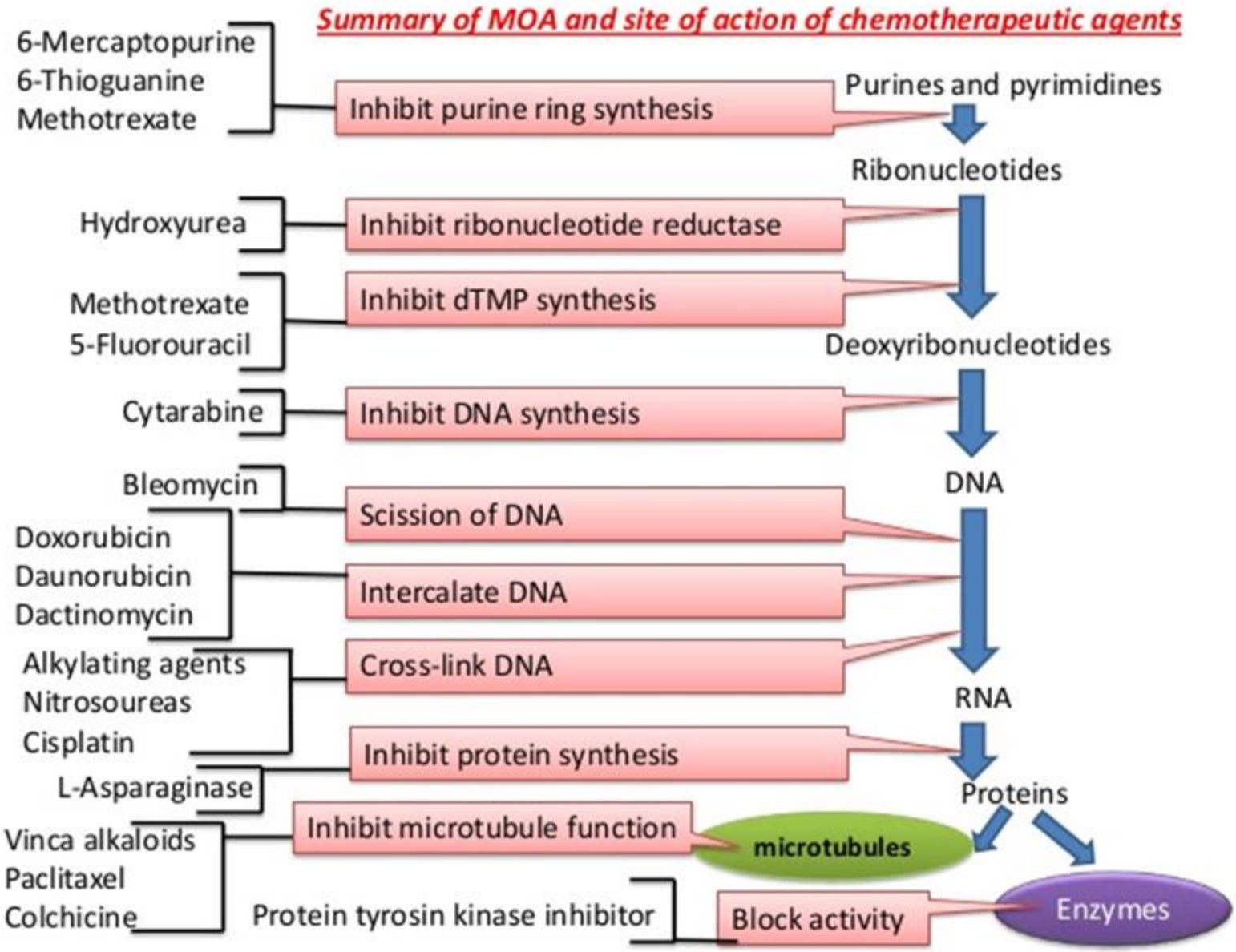
Growth Fraction

Cytotoxic drugs are more effective against tumors that have a high growth fraction (large percentage actively dividing). Normal cells with high growth fraction (e.g., bone marrow) are also more sensitive to anticancer drugs

Rapidly proliferating cells such as the bone marrow, gastrointestinal tract mucosa, hair follicles, and gonads are the most sensitive to cytotoxic drugs. Most often bone marrow suppression (BMS) is dose-limiting

Cytotoxic drugs

Cell Cycle-Specific (CCS) Agents	Cell Cycle-Nonspecific (CCNS) Agents
Antimetabolites: - Cytarabine - Fluorouracil -Mercaptopurine - Methotrexate	Alkylating agents: - Busulfan - Carmustine - Cyclophosphamide - Mechlorethamine
- Bleomycin	- Dactinomycin
- Etoposide - Teniposide	- Irinotecan - Topotecan
- Paclitaxel	- Cisplatin
Vinca alkaloids: - Vinblastine - Vincristine	Anthracyclines: - Daunorubicin - Doxorubicin


Summary of MOA and site of action of chemotherapeutic agents
6-Mercaptopurine
6-Thioguanine
Methotrexate
Inhibit purine ring synthesis
Purines and pyrimidines
Ribonucleotides
Hydroxyurea
Inhibit ribonucleotide reductase
Methotrexate
5-Fluorouracil
Inhibit dTMP synthesis
Deoxyribonucleotides
Cytarabine
Inhibit DNA synthesis
DNA
Bleomycin
Scission of DNA
Doxorubicin
Daunorubicin
Dactinomycin
Intercalate DNA
Alkylating agents
Nitrosoureas
Cisplatin
Cross-link DNA
RNA
L-Asparaginase
Inhibit protein synthesis
Proteins
Vinca alkaloids
Paclitaxel
Colchicine
Inhibit microtubule function
microtubules
Protein tyrosin kinase inhibitor
Block activity
Enzymes

Resistance to anticancer drugs

Causes

1. **Poor drug absorption** & delivery
2. Increase **drug efflux** out of cell (through MDR-gene and P-glycoprotein)
3. **Mutations or deletions in drug targets.**
4. **Loss of function** (by mutation) of the tumor suppressor gene; **p53**.
5. Expressing an **alternative molecules** (bypasses the target &/or stimulates proliferation).

To avoid resistance

- Use **combination therapy**
- Use **maximal tolerated dose**.
- Drug regimen are repeated in **multiple cycles** to kill most tumor cells
- Consider the **pharmacokinetic parameters** : e.g., Monitoring of drug levels in plasma to achieve a target plasma concentration.
- **Molecular testing,** if possible, to identify patients likely to benefit from treatment and those who will be resistant before start to therapy.

General toxicity of anticancer drugs

1-Bone marrow suppression: neutropenia, anemia and thrombocytopenia.

2- Nausea and vomiting.

3- GIT toxicity: Damage of mucosal lining from the mouth through the gastrointestinal tract leading to ulcers, oral mucositis, **anorexia** and hemorrhagic enteritis & diarrhea.

4- Skin toxicity: Hyperpigmentation, alopecia, photosensitivity, nail changes and generalized rashes.

5- Gonads: sterility, teratogenicity and mutagenicity.

6- Hyperuricemia due to cytotoxic-induced malignant tissue destruction.

7- Hypercalcemia.

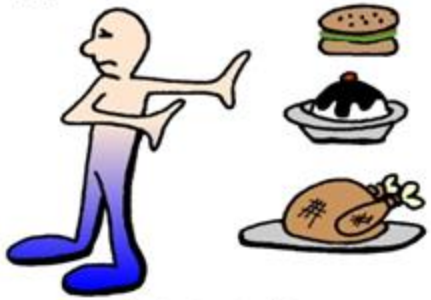
8- Fetal malformation if given during pregnancy.

9- Lymphoid tissue: lymphocytopenia and immunosuppression with consequent secondary infection.

ANTICANCER DRUGS
ADVERSE REACTIONS/PRECAUTIONS

Bone Marrow Suppression

Nausea and Vomiting



Anorexia

GI Disturbances

Alopecia

Avoid Pregnancy

To reduce bone marrow (BM) toxicity

- Pulse courses / 3-4 weeks rather than daily dosing. This allows BM recovery.

- Administration of granulocyte colony-stimulating factor 24-72 h after cytotoxic chemotherapy to avoid granulocytopenia.

- Administration of erythropoiesis-stimulating agents reduces anemia of cytotoxic drugs. **Uncontrolled hypertension is contraindication for its use.**

To reduce nausea and vomiting

1-Ondansetron (5-HT3 receptor blocker) is more effective in resistant vomiting.
2- **Aprepitant** (NK1 receptor blocker).
3- **Dexamethasone**.
4- **Lorazepam** are effective either alone or better in combination.
5-Tetrahydocanabinol.

1- Antimetabolites

- These drugs are structural analogues to important precursors of nucleic acid synthesis.
- These drugs inhibit nucleotide synthesis or compete with them for DNA or RNA.
- These drugs are CCS on (S phase).
- There are three major classes:

A. Folic acid analogues

- Methotrexate

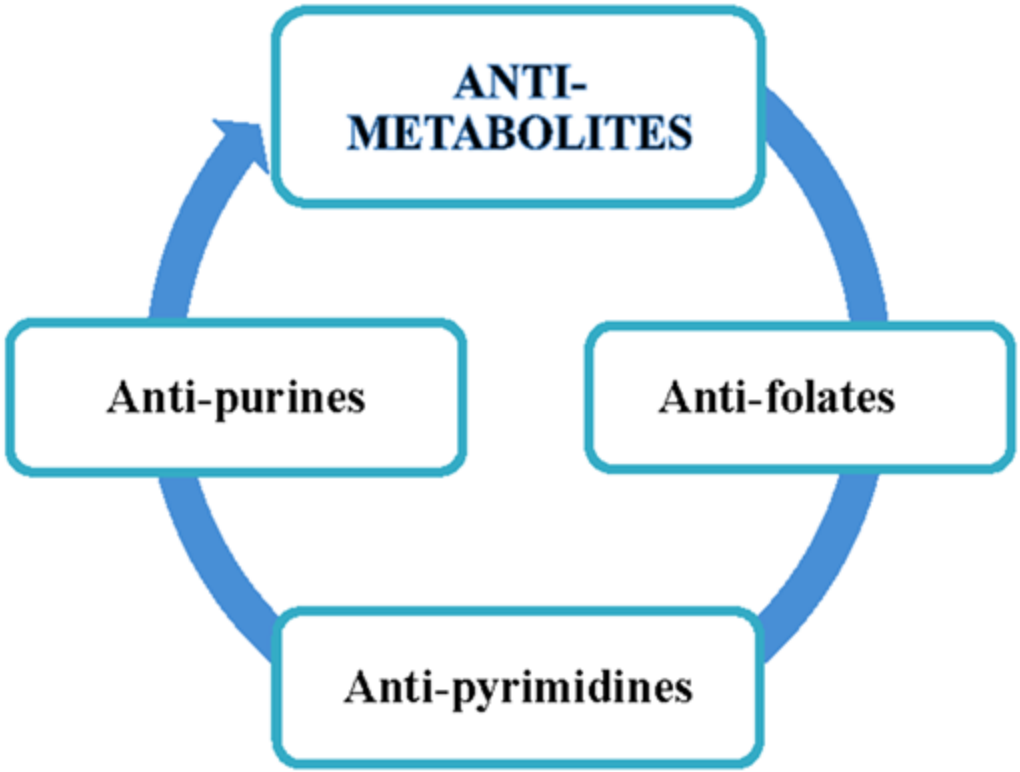
B. Purine analogues

- Thiopurines

C. Pyrimidine analogues

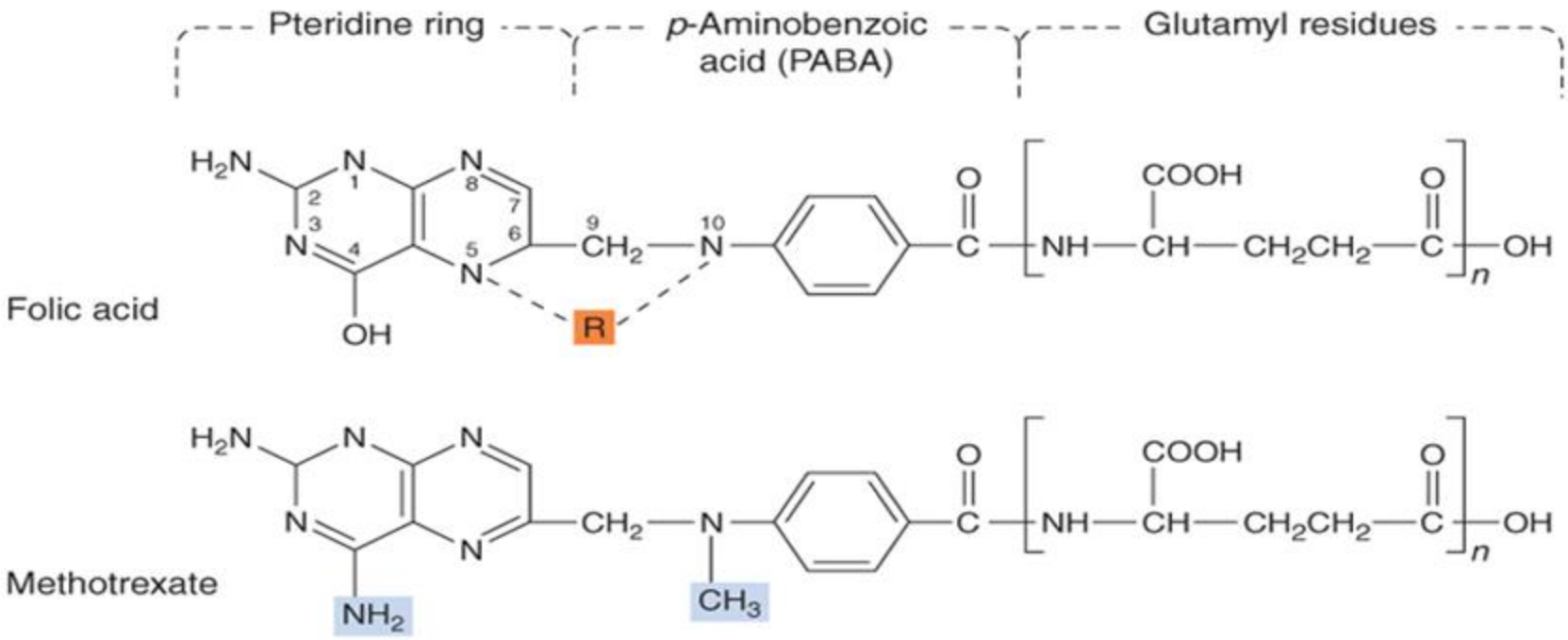
-5-Flurouracil

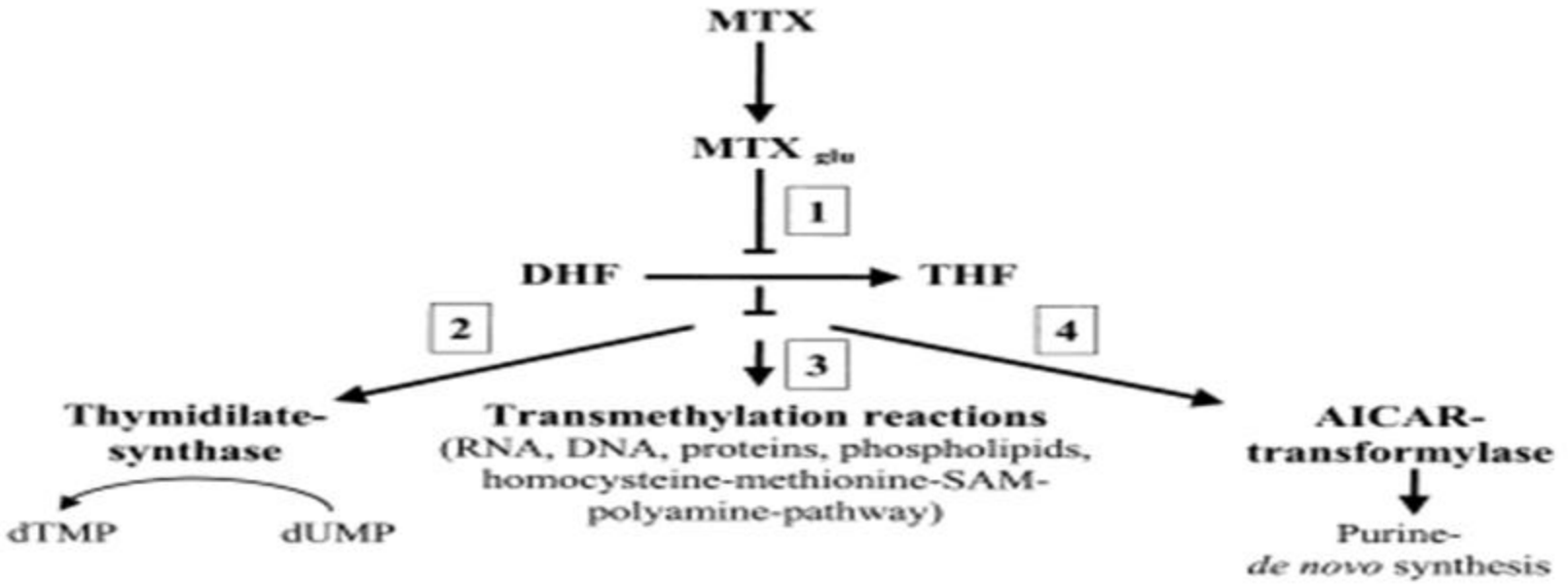
-Ara-C

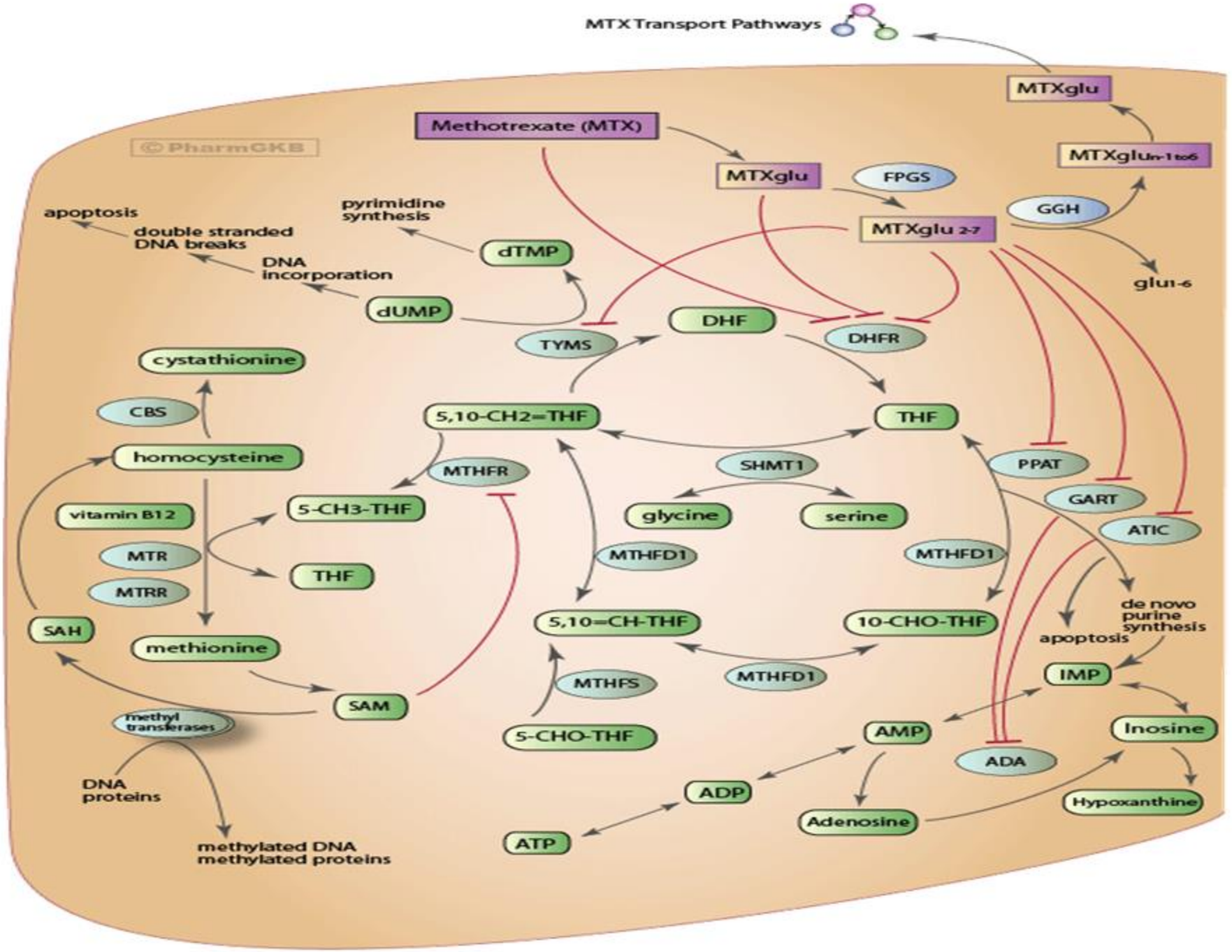


1- Methotrexate (MTX)

- ❑ Structurally related to folic acid
- ❑ MTX inhibits dihydrofolate reductase (DHFR), the enzyme that converts folic acid to its active tetrahydrofolic acid (FH4)
- ❑ In both normal and tumor cells, MTX undergoes conversion into poly-glutamates **(MTX-PGs)** which **inhibits thymidylate synthase** enzyme and other enzymes involved in **purine synthesis.**
- ❑ This leads to ↓ DNA, RNA & protein synthesis and cell death (Cytotoxicity).
- ❑ MTX is effective against rapidly proliferating or dividing tumor and normal cells like intestinal epithelium and bone marrow.
- ➢ MTX is used in combination with other anticancer drugs for **Acute lymphocytic leukemia (ALL), Choriocarcinoma,** Burkitt lymphoma in children, Breast cancer and in Head & neck carcinoma.
- ➢ MTX used in smaller doses as DMARDs for treating sever **psoriasis** and **rheumatoid arthritis.**


Pteridine ring
p-Aminobenzoic acid (PABA)
Glutamyl residues
Folic acid
Methotrexate
R
NH2
CH3


MTX
MTX glu
1
DHF
THF
2
3
4
Thymidilate-synthase
dTMP
dUMP
Transmethylation reactions
(RNA, DNA, proteins, phospholipids, homocysteine-methionine-SAM-polyamine-pathway)
AICAR-transformylase
Purine-de novo synthesis


MTX Transport Pathways
MTXglu
Methotrexate (MTX)
MTXglu
FPGS
MTXglu n-1 to 6
GGH
MTXglu 2-7
glu1-6
© PharmGKB
apoptosis
double stranded DNA breaks
DNA incorporation
pyrimidine synthesis
dTMP
dUMP
TYMS
DHF
DHFR
cystathionine
CBS
homocysteine
5,10-CH2=THF
THF
MTHFR
SHMT1
PPAT
GART
ATIC
vitamin B12
MTR
MTRR
5-CH3-THF
THF
glycine
serine
MTHFD1
MTHFD1
SAH
methionine
SAM
5,10=CH-THF
10-CHO-THF
MTHFD1
de novo purine synthesis
apoptosis
IMP
MTHFS
5-CHO-THF
methyl transferases
AMP
Inosine
ADA
DNA proteins
ADP
Hypoxanthine
Adenosine
ATP
methylated DNA
methylated proteins

Resistance to MTX:

1. ↓transport of MTX into the cell
2. Production of an altered form of DHFR
3. Increase concentration of DHFR
4. Decreased ability to synthesize MTX polyglutamate
5. ↑ expression of multidrug resistant protein (MRP) which ↑ MTX efflux

❑To overcome resistance, **high dose of MTX** may permit **entry** of the drug into malignant cells.

❑To avoid toxicity from high dose MTX administration, a fully reduced folate coenzyme called **leucovorin** (folinic acid) is concomitantly given . It repletes the intracellular pool of FH4 cofactors mainly in normal cells (**leucovorin rescue**).

❑**MTX needs therapeutic drug monitoring (TDM) to avoid toxicity and to calculate** leucovorin doses.

Toxicity of methotrexate

1-Nephrotoxicity (avoided by drinking plenty of water & alkalinization of urine).
2-Bone marrow suppression
3-Mucosal ulcerations of GIT, Nausea and vomiting.
4- **Hepatotoxicity & liver fibrosis on long use (for autoimmune diseases)**
5-**Teratogenecity.**

Precautions during use of high dose MTX

Vigorous hydration and **alkalinization of urine** to prevent MTX precipitation and avoid nephrotoxicity.
Administration of **leucovorin.**
Laboratory follow-up during chronic use of MTX:
A- Complete blood count (CBC) should be monitored.
B-Liver function tests to identify early hepatic fibrosis (liver biopsy or fibroscan may be also needed).
C-T.D.M. for MTX levels
C-Renal functions and urine analysis.

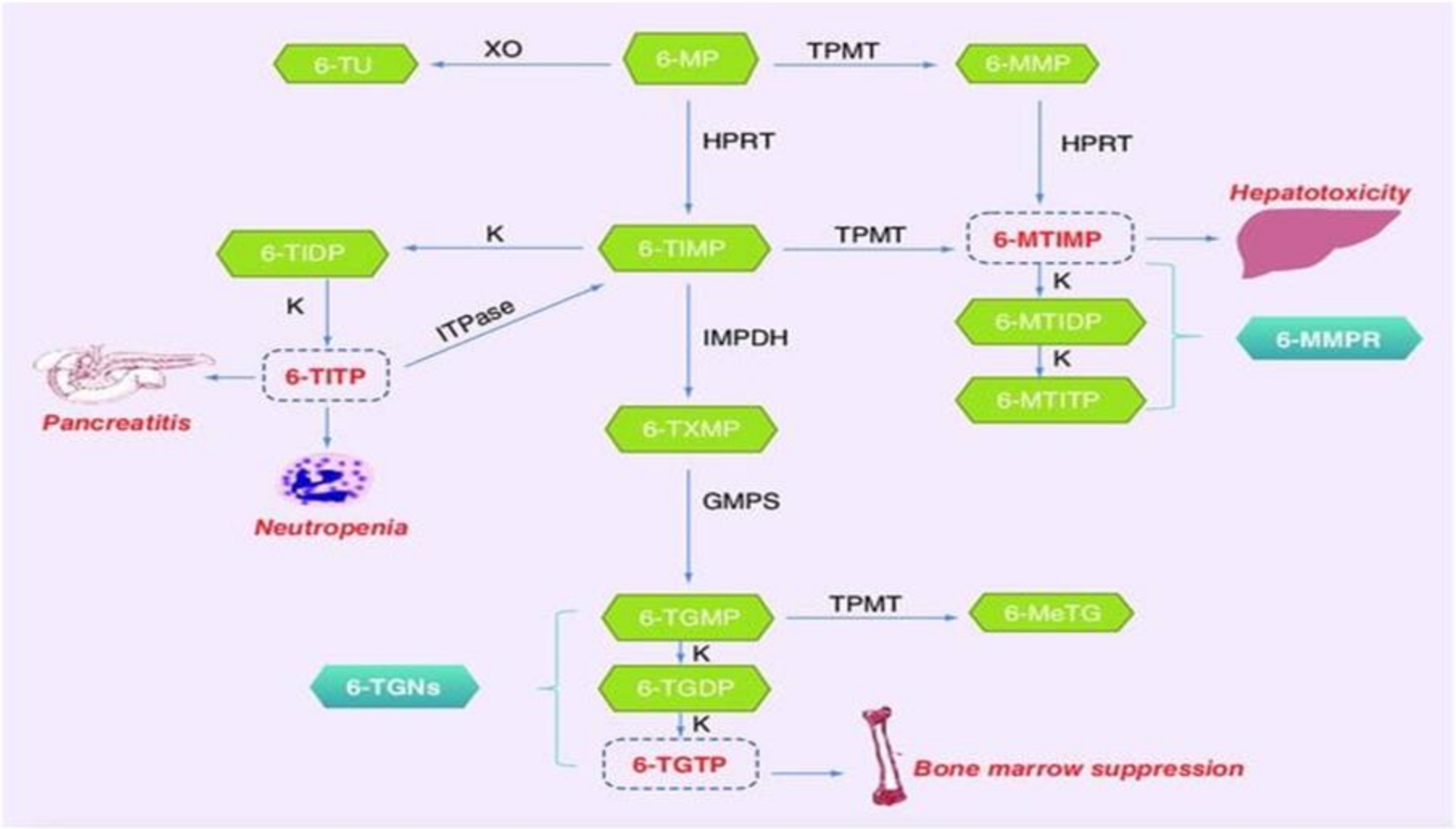
2- Thiopurines

6- mercaptopurine (6-MP) & 6- Thioguanine (6-TG)

- These purine analogues **inhibit *de novo* purine synthesis (act on S phase)** through their active intracellular metabolites (via IMPDH and HGPR transferase).
  - 6-MP is used in **maintenance of remission in acute lymphoblastic leukemia.**
  - 6-TG is used in **treatment of acute non lymphocytic leukaemia.**
  - **They can be used for autoimmune diseases.**
- 6-MP is deactivated by **xanthine oxidase** & **thiopurine methyl transferase** (TPMT).
- Genetic polymorphisms in TPMT enzyme causes individual variations in 6-MP levels.
- Patients who have a low expression of TPMT enzyme are associated with good response, increased drug toxicity (Bone Marrow Suppression). High TPMT expression may cause relapse of leukemia.

Drug interactions of thiopurines

- Allopurinol, a xanthine oxidase inhibitor when given with 6-MP to treat the secondary hyperuricemia produces a prominent increase in 6-MP toxicity. Therefore, dose of 6-MP may be reduced by 50% when concomitantly given with this drug.



6-Mercaptopurine

Xanthine oxidase

inhibits

Allopurinol

Degradation products for excretion

Fluorouracil (5-FU)

- 5-FU (pyrimidine analogue) is converted to active metabolites (e.g., 5-FUTP) which inhibits thymidylate synthase and thus inhibits DNA and RNA synthesis (CCS on S phase).
- 5-FUTP is then converted to 5-FdUTP which is phase nonspecific, killing cells not only in S phase, but through out the cell cycle.
- 5-FU is used in treatment of slowly growing solid tumors (**colorectal**, breast, ovarian, **pancreatic** & **gastric carcinomas**).
- Topical 5-Fu is used for treating **vitiligo, keratoses** & **basal cell carcinoma.**
- Capecitabine is a prodrug to 5-FU with the same mechanism & uses.
- Pharmacogenetics: The dihydropyrimidine dehydrogenase (DPD) enzyme is responsible for the metabolism of capecitabine and 5-fluorouracil is polymorphic. DPD deficiency have a significantly increased risk of severe or even fatal drug toxicities.

Cytosine arabinoside (Cytarabine)

Ara-C (Arabinofuranosyl cytidine)

- Its is activated by intracellular kinases to Ara-CTP (cytosine arabinoside triphosphate) which **inhibits DNA synthesis** leading to cell death.
- It is an **S-phase-specific agent**
- Major clinical use is acute **myeloid & other types of leukemia and lymphomas.**
- Cytarabine has some antiviral activity (may be used for the treatment of generalized herpesvirus infection). However, severe bone marrow depression limits the use of Ara-C as antiviral.
- Adverse effects: Pancytopenia, GIT mucositis, pancreatitis and rarely, myelopathy after high dose or frequent intrathecal Ara-C administration.
- To prevent the side effects and improve the therapeutic efficiency, various derivatives of these drugs (including amino acid, peptide, fatty acid and phosphates) have been evaluated,

Thymineless death

- Thymineless death of cells (bacteria, yeasts & mammalian cells) is a phenomenon where cell death occurs due to significant depletion of thymidine triphosphate (dTTP), an essential precursor for DNA replication.

- This phenomenon underlies the mechanism of action of several antibacterial, antifungal, antimalarial and anticancer agents, such as trimethoprim, sulfamethoxazole, flucytosine, methotrexate and fluorouracil.


Thank You!