# Anticancer Drugs
# Part 2

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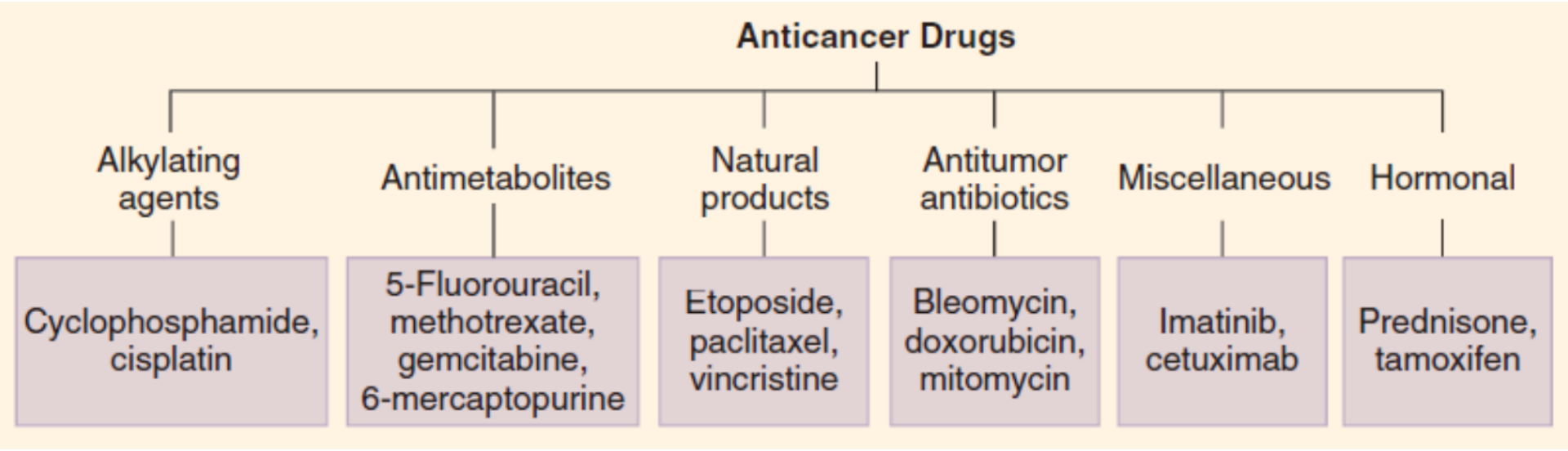
Pharmacology 3


Anticancer Drugs
Alkylating agents
Cyclophosphamide, cisplatin
Antimetabolites
5-Fluorouracil, methotrexate, gemcitabine, 6-mercaptopurine
Natural products
Etoposide, paclitaxel, vincristine
Antitumor antibiotics
Bleomycin, doxorubicin, mitomycin
Miscellaneous
Imatinib, cetuximab
Hormonal
Prednisone, tamoxifen

# Antimetabolites

- Structurally related to normal compounds that exist within the cell.
- They generally interfere with the availability of purine or pyrimidine nucleotide precursors, either by:
  - inhibiting their synthesis
  - or by competing with them in DNA or RNA synthesis.

- Maximal cytotoxic effects are in S-phase (cell-cycle specific).

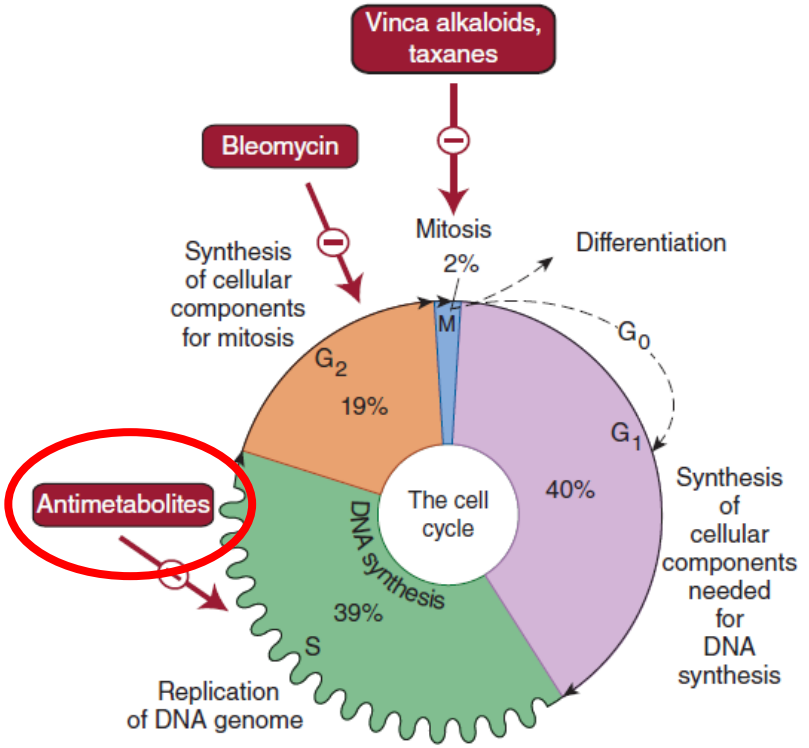



**FIGURE 54–1** Phases of the cell cycle that are susceptible to the actions of cell cycle-specific (CCS) drugs. All dividing cells—normal and neoplastic—must traverse these cell cycle phases before and during cell division. Tumor cells are usually most responsive to specific drugs (or drug groups) in the phases indicated. Cell cycle-nonspecific (CCNS) drugs act on tumor cells while they are actively cycling and while they are in the resting phase ($G_0$). (Reproduced and modified, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 12th ed. McGraw-Hill, 2012: Fig. 54–2.)

# Antimetabolites
# (Cell cycle specific)

## Folate Antagonist

- Methotrexate
- Pemetrexed
- Pralatrexate

## Purine Antagonists

(adenine and guanine)

- 6-thioguanine
- 6-mercaptopurine
- Fludarabine

## Pyrimidine Antagonists

(thymidine, cytosine, and uracil)

- 5-fluorouracil
- Capecitabine
- Cytarabine (cytosine arabinoside)
- Gemcitabine

# Methotrexate

**Mechanism of action:**

- Methotrexate (MTX) is a folic acid analog that binds with high affinity to the active site of **dihydrofolate reductase (DHFR).**
- This results in inhibition of the synthesis of tetrahydrofolate (THF), the key one-carbon carrier for enzymatic processes involved in de novo synthesis of:
  - Thymidylate
  - purine nucleotides
  - amino acids serine and methionine
- Inhibition of these metabolic processes thereby interferes with the formation of DNA, RNA, and key cellular proteins.

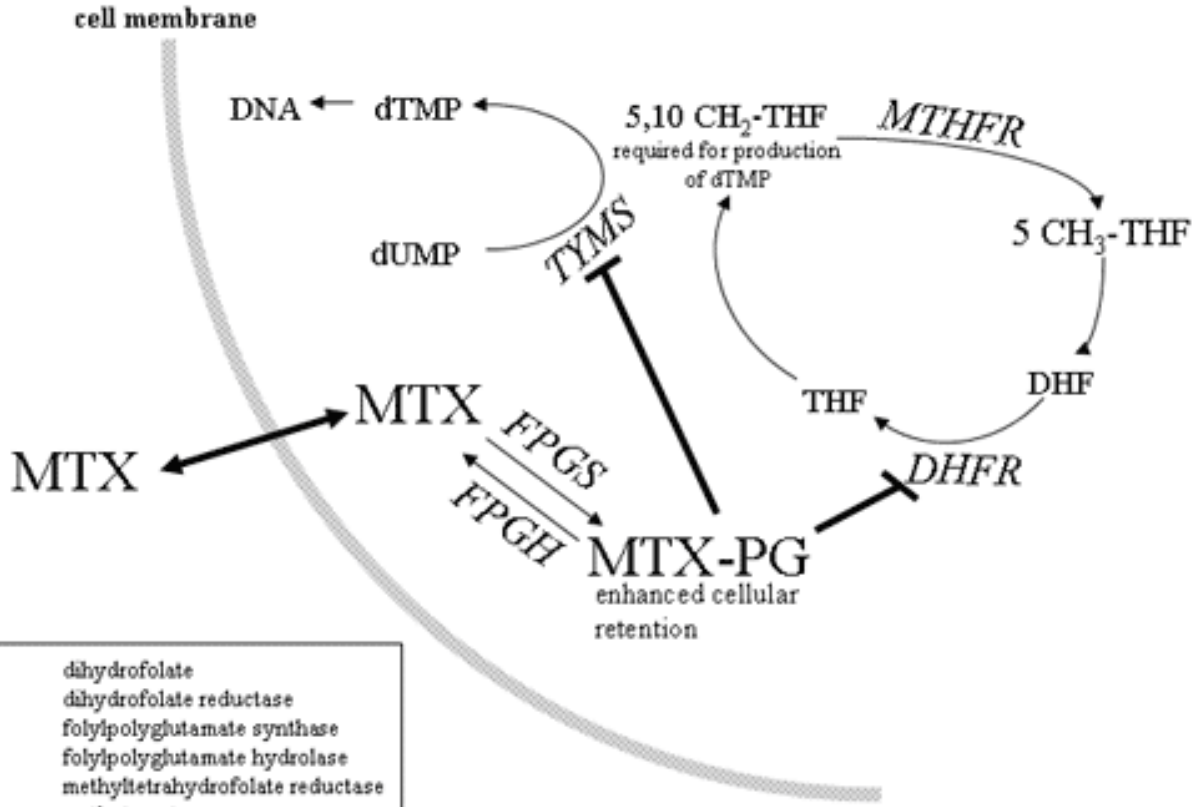
# Methotrexate

- MTX is transported into the cell via the **reduced folate carrier**.
- Intracellular formation of **polyglutamate metabolites**, with the addition of up to 5–7 glutamate residues, is critically important for the therapeutic action of MTX, and this process is catalyzed by the enzyme **folylpolyglutamate synthase (FPGS).**
- MTX polyglutamates inhibit:

1. Enzymes involved in purine nucleotide synthesis
2. Enzymes involved in thymidylate synthesis

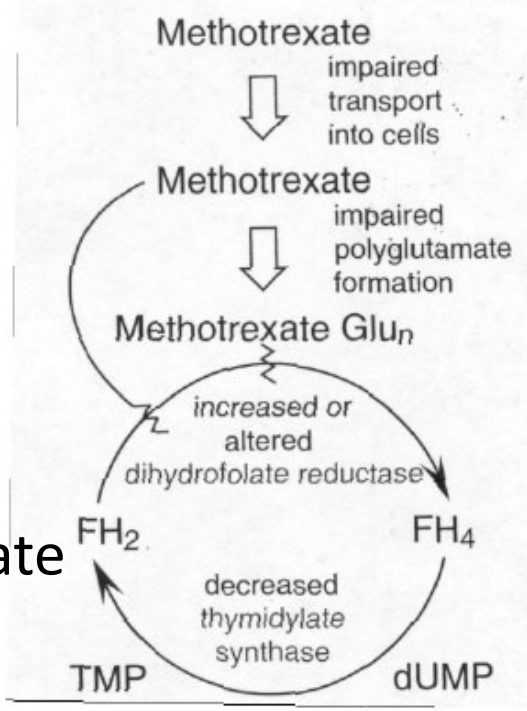
# Methotrexate cellular pharmacology

targets for pharmacogenetic analysis shown in italics




| | |
|---|---|
| DHF | dihydrofolate |
| DHFR | dihydrofolate reductase |
| FPGS | folylpolyglutamate synthase |
| FPGH | folylpolyglutamate hydrolase |
| MTHFR | methyltetrahydrofolate reductase |
| MTX | methotrexate |
| MTX-PG | methotrexate polyglutamate |
| THF | tetrahydrofolate |
| 5 $CH_3$-THF | methyl-THF |
| 5,10 $CH_2$-THF | methylene-THF |
| TYMS | thymidylate synthase |

# Methotrexate Resistance




- Several resistance mechanisms to MTX have been identified, and they include:

  (1) decreased drug transport via the reduced folate carrier

  (2) decreased formation of cytotoxic MTX polyglutamates,

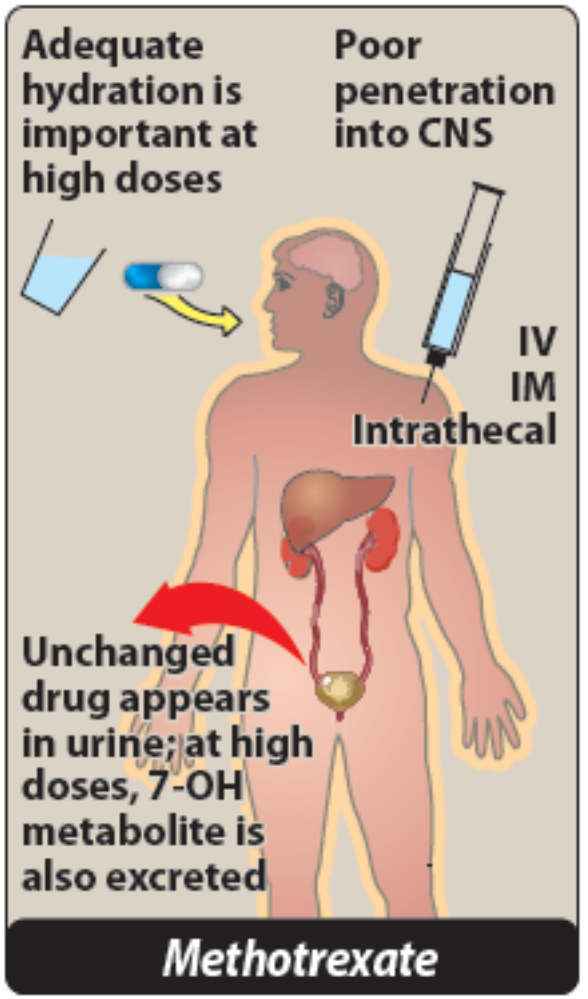
  (3) increased levels of the target enzyme DHFR through gene amplification and other genetic mechanisms

  (4) altered DHFR protein with reduced affinity for MTX.

  (5) decreased accumulation of drug through activation of the multidrug resistance transporter P170 glycoprotein.

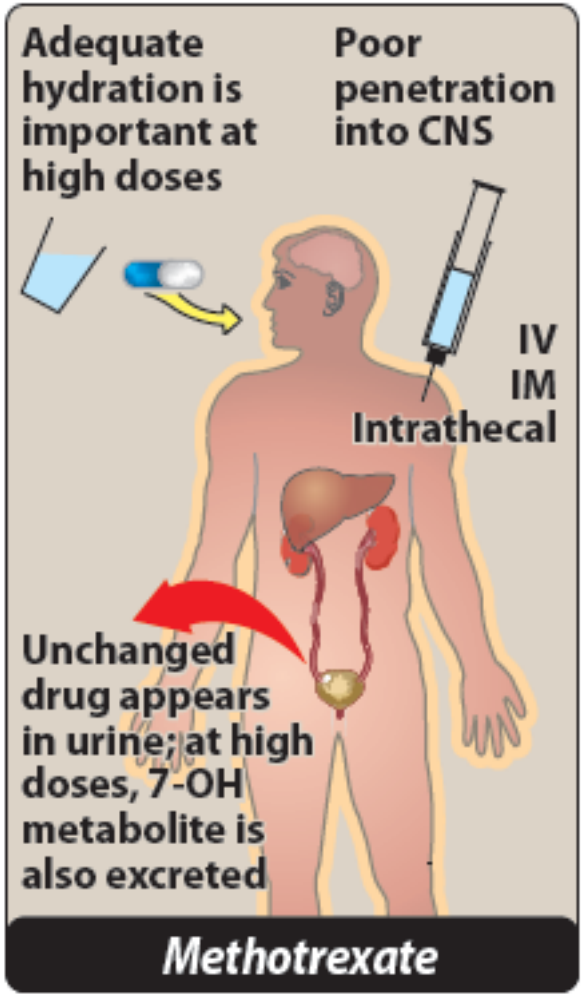
# Pharmacokinetics of MTX

- MTX is administered by the intravenous, intrathecal, or oral route.
- **Renal excretion** is the main route of elimination and is mediated by glomerular filtration and tubular secretion. As a result, dose modification is required in the setting of renal dysfunction.
  - Care must also be taken when MTX is used in the presence of drugs such as aspirin, nonsteroidal anti-inflammatory agents, penicillins, and cephalosporins, as these agents inhibit the renal excretion of MTX.



# Adverse effects of MTX

- High doses of MTX undergo hydroxylation at the 7-position. This derivative is much less active, less water soluble and may lead to **crystalluria**.
- Therefore, it is important to keep the urine alkaline and the patient well hydrated to avoid renal toxicity.



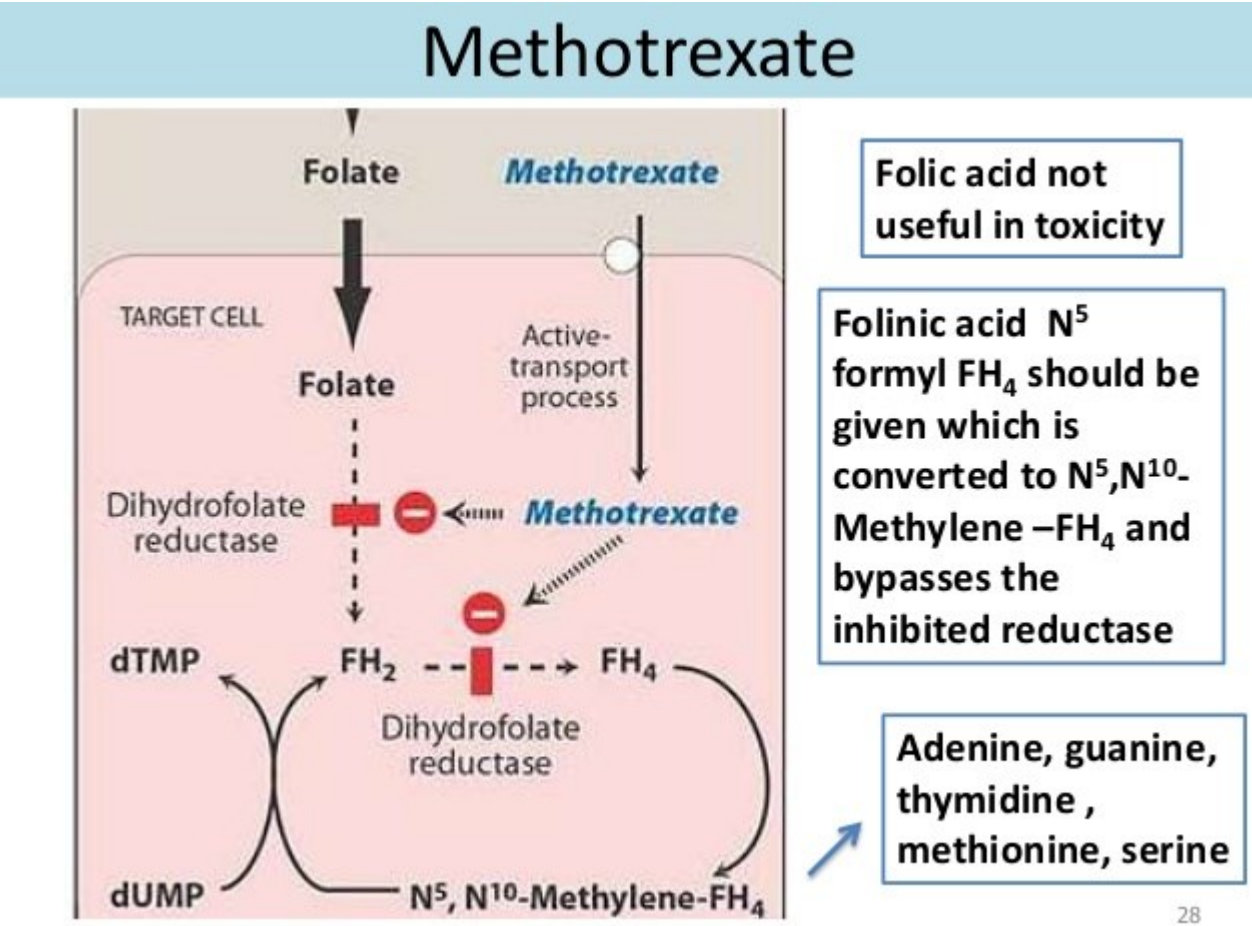
# Adverse effects of MTX

- Nausea, vomiting, and diarrhea, stomatitis, myelosuppression with neutropenia and thrombocytopenia.
- The adverse effects of MTX can be reversed by administration of the reduced folate **leucovorin** (5-formyltetrahydrofolate) or by L-leucovorin (which is the active enantiomer). Leucovorin is taken up more readily by normal cells than by tumor cells.

# Adverse effects of MTX

- **Leucovorin** rescue is used in conjunction with high-dose MTX therapy to rescue normal cells from excessive toxicity, and it has also been used in cases of accidental drug overdose.
- However, doses of leucovorin must be kept minimal to avoid possible interference with the antitumor action of MTX.
- Contraindications: It should be avoided in pregnancy.

# Adverse effects of MTX




**Folic acid not useful in toxicity**

**Folinic acid $N^5$ formyl $FH_4$ should be given which is converted to $N^5$,$N^{10}$-Methylene –$FH_4$ and bypasses the inhibited reductase**

**Adenine, guanine, thymidine , methionine, serine**

# Methotrexate (MTX)

Therapeutic uses:

- MTX is used usually in combination with other drugs
- Effective against breast cancer, head and neck cancer, osteogenic sarcoma, primary central nervous system lymphoma, non-Hodgkin’s lymphoma, bladder cancer, choriocarcinoma.
- Low-dose MTX is effective as a single agent against certain inflammatory diseases, such as severe psoriasis and rheumatoid arthritis as well as Crohn's disease.

# Other Antifolate Drugs

1. **Pemetrexed**

- Pemetrexed is an antifolate analog with activity in the S phase of the cell cycle. As in the case of MTX, it is transported into the cell via the reduced folate carrier and requires activation by FPGS to yield higher polyglutamate forms.
- While this agent targets DHFR and enzymes involved in de novo purine nucleotide biosynthesis, its main mechanism of action is inhibition of thymidylate synthase (TS).

# Other Antifolate Drugs

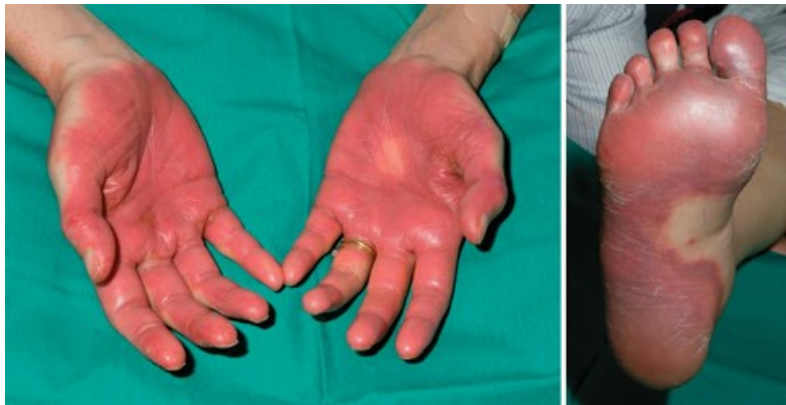
**1. Pemetrexed**

- As with MTX, pemetrexed is mainly excreted in the urine, and dose modification is required in patients with renal dysfunction.
- Of note, vitamin supplementation with folic acid and vitamin $B_{12}$ appears to reduce the toxicities associated with pemetrexed, while not interfering with clinical efficacy.

# Other Antifolate Drugs

**1. Pemetrexed**

- The main adverse effects include myelosuppression, skin rash, mucositis, diarrhea, fatigue, and **hand-foot syndrome**.
- The hand-foot syndrome is manifested by painful erythema and swelling of the hands and feet.
- Pretreatment with corticosteroids (i.e. dexamethasone) is recommended to reduce the incidence and severity of this toxicity.



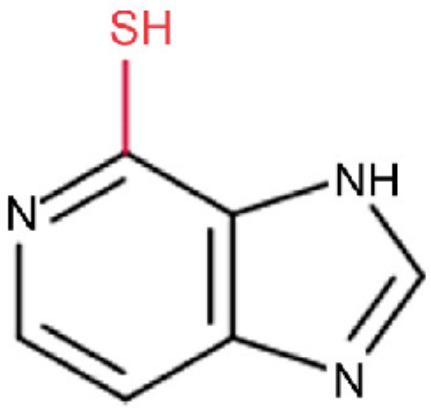
# Other Antifolate Drugs

**2. Pralatrexate**

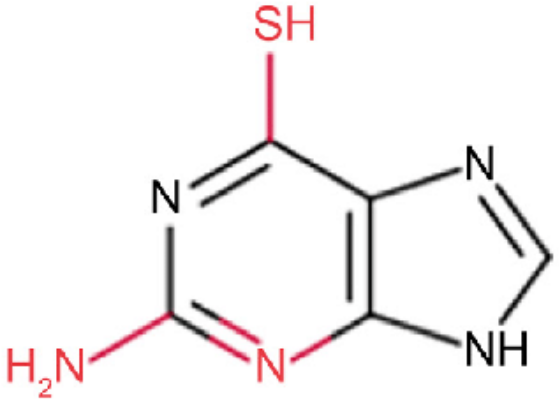
- PK and PD are similar to pemetrexed.
- Does not cause Hand-foot syndrome
- Vitamin supplementation with folic acid and vitamin $B_{12}$ appear to reduce the toxicities associated with pralatrexate, while not interfering with clinical efficacy.

# Purine antagonists

**6-mercaptopurine**

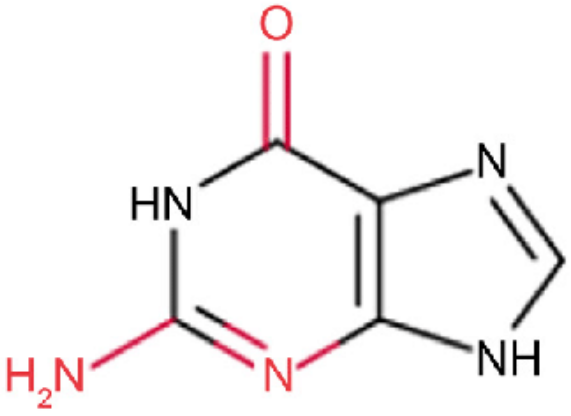



**Thioguanine**




**Adenine**

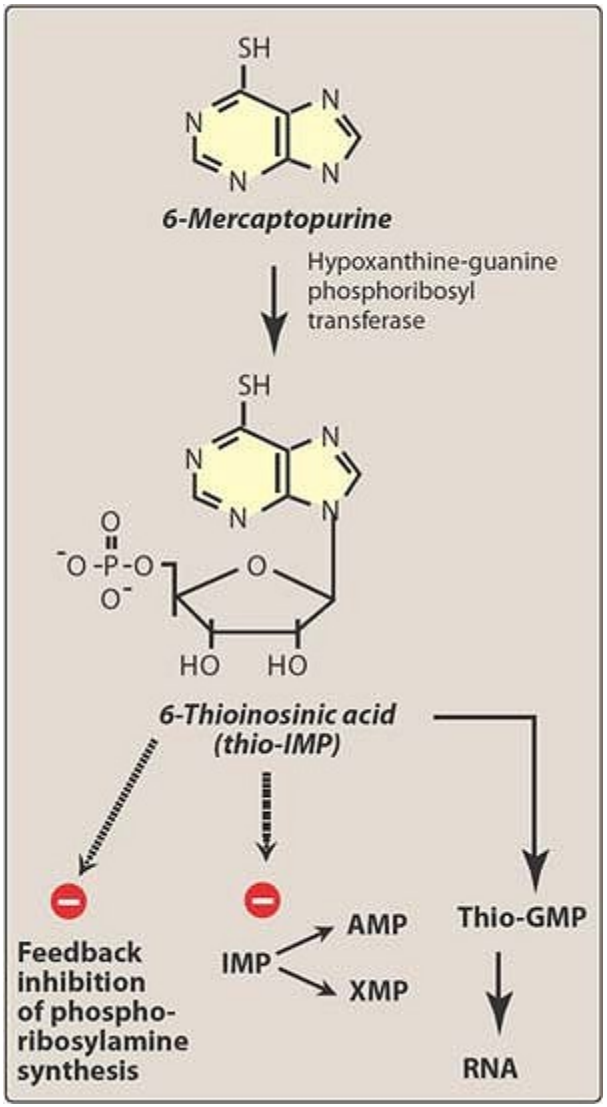

**Guanine**



# Purine antagonists
# 6-Mercaptopurine (6-MP)

**Mechanism of action:**

- 6-MP is inactive in its parent form and must be metabolized **by hypoxanthine-guanine phosphoribosyl transferase (HGPRT)** to form the monophosphate nucleotide 6-thioinosinic acid (thio-IMP), which in turn inhibits several enzymes of de novo purine nucleotide synthesis.
- The monophosphate form is eventually metabolized to the triphosphate form, which can then be incorporated into both RNA and DNA. (nonfunctional RNA and DNA).



# 6-MP

**Resistance:**

- Decreased levels of HGPRT (for example, in Lesch-Nyhan syndrome)
- Increased dephosphorylation,
- Increased metabolism of the drug to thiouric acid.

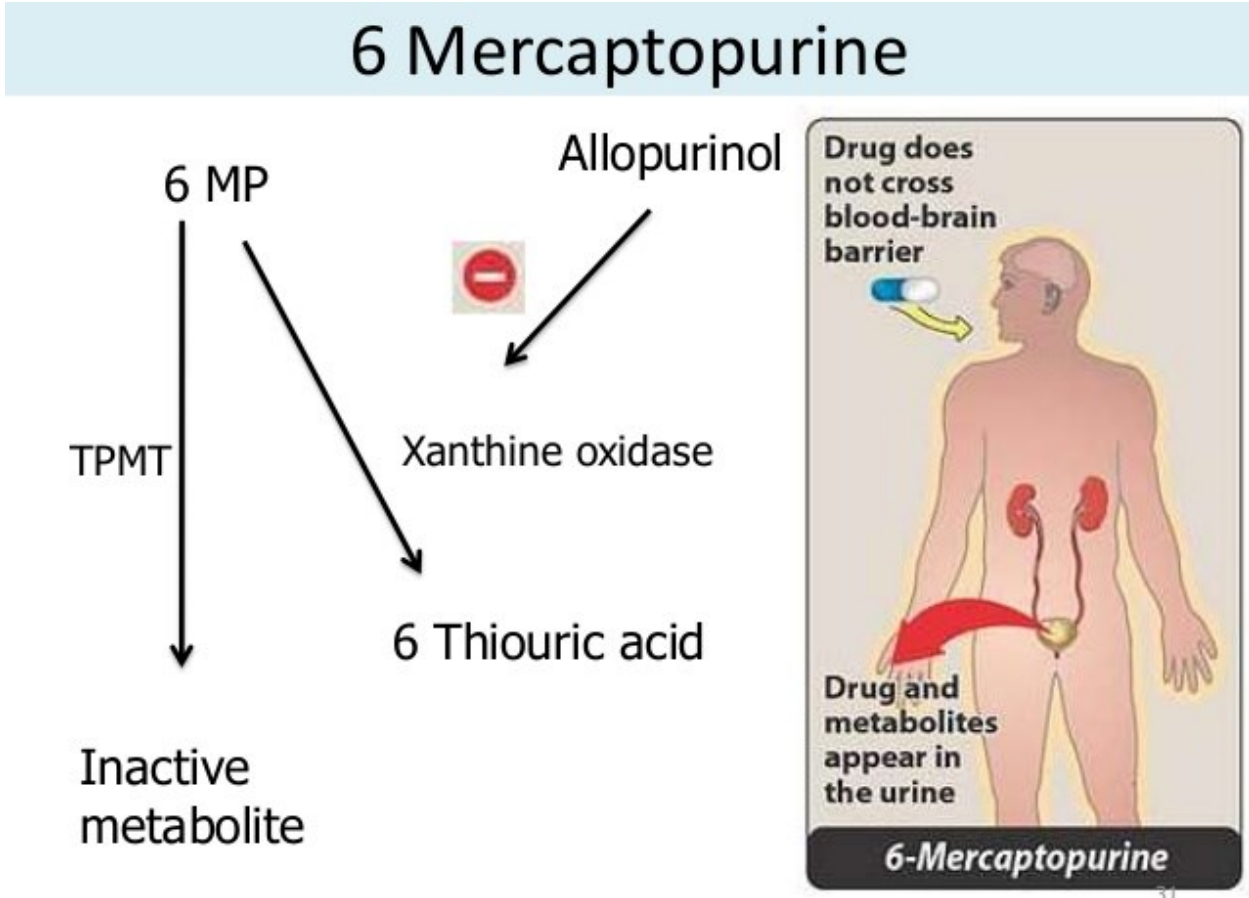
**Adverse effects:**

- Myelosuppression, immunosuppression, and hepatotoxicity.

# 6-MP

**Pharmacokinetics:**

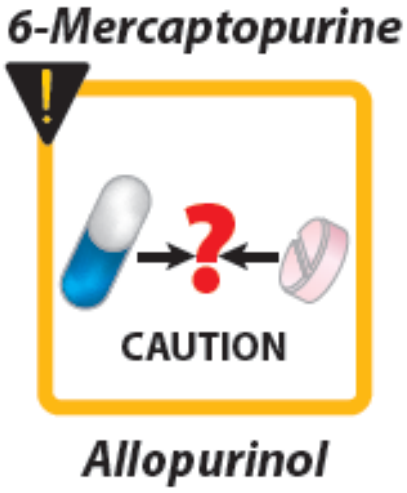
- Administered orally. The bioavailability of 6-MP can be reduced by the first-pass metabolism in the liver
- 6-MP is converted to an inactive metabolite (6-thiouric acid) by an oxidation reaction catalyzed by xanthine oxidase.
- The parent drug and its metabolites are excreted by the kidney.



# 6-MP

**Drug-Drug interactions:**

- **Allopurinol, a potent xanthine oxidase inhibitor,** is frequently used as a supportive care measure in the treatment of acute leukemias to prevent the development of hyperuricemia that often occurs with tumor cell lysis.
- Because allopurinol inhibits xanthine oxidase, simultaneous therapy with allopurinol and 6-MP would result in increased levels of 6-MP, thereby leading to excessive toxicity. In this setting, the dose of mercaptopurine must be reduced by 50–75%.



# Other Purine Antagonists

## 6-Thioguanine (6-TG)

- **6-TG** also inhibits several enzymes in the de novo purine nucleotide biosynthetic pathway.
- 6-TG is metabolized by deamination (not oxidation by xanthine oxidase). This is an important issue because 6-TG does not interact with allopurinol such as 6-MP. 6-TG can be used in full doses with allopurinol.
- The side effect profile is similar to 6-MP (myelosuppression, immunosuppression, and hepatotoxicity).

# Other Purine Antagonists

**Fludarabine**

- The main dose-limiting toxicity is myelosuppression.
- This agent is a potent **immunosuppressant** with inhibitory effects on CD4 and CD8 T cells. Patients are at increased risk for opportunistic infections, including fungi, herpes, and *Pneumocystis jiroveci* pneumonia (PCP). Patients should receive PCP prophylaxis with trimethoprim-sulfamethoxazole (double strength) at least three times a week, and this should continue for up to 1 year after stopping fludarabine therapy.

# Other Purine Antagonists

**Cladribine**

- It is normally administered as a single continuous 7-day infusion; under these conditions, it has a very manageable safety profile with the main toxicity consisting of transient myelosuppression.
- As with other purine nucleoside analogs, it has immunosuppressive effects, and a decrease in CD4 and CD8 T cells, lasting for over 1 year, is observed in patients.

Questions??