

Anticancer Drugs

Part 2

Heba Khader, Ph.D
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.

antifolate

Antipurine
Pyrimidine

ممنوع تصنيع الـ purine
pyrimidine

الـ purine
pyrimidine
ممنوع تصنيع الـ purine
pyrimidine

DNA synthesis & DNA elongation

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

الـ purine
pyrimidine
ممنوع تصنيع الـ purine
pyrimidine

DNA

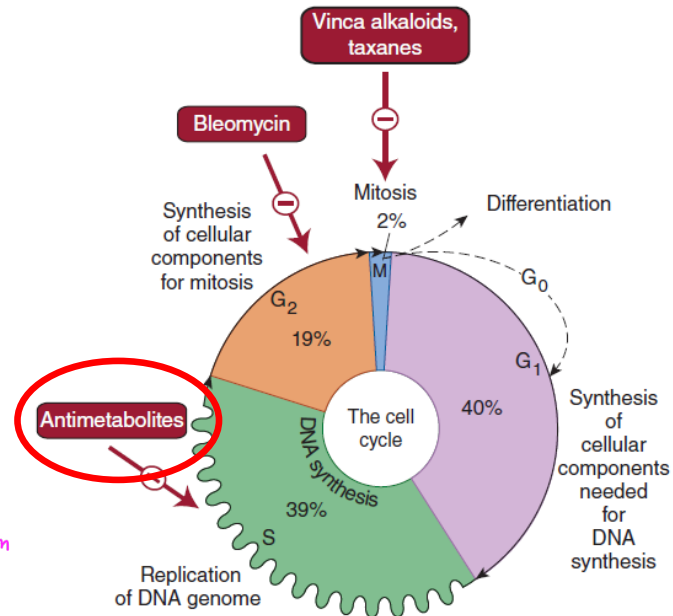


FIGURE 54-1 Phases of the cell cycle that are susceptible to the actions of cell cycle-specific (CCS) drugs. All dividing cells—normal and neoplastic—must traverse these cell cycle phases before and during cell division. Tumor cells are usually most responsive to specific drugs (or drug groups) in the 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.)

metabolite حين بالظلية
لا يمكن إنتاج البروتينات
metabolite
pyrimidine + purine

Antimetabolites

(Cell cycle specific)

①

Folate Antagonist antifolate

- Methotrexate
- Pemetrexed
- Pralatrexate

②

Purine Antagonists antipurine

(adenine and guanine)

- 6-thioguanine
- 6-mercaptopurine
- Fludarabine

③

Pyrimidine Antagonists part 3

(thymidine, cytosine, and uracil)

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



Methotrexate

Mechanism of action:

- This results in inhibition of the synthesis of tetrahydrofolate (THF), the key one-carbon carrier for enzymatic processes involved in de novo synthesis of:

① – Thymidylate

② – purine nucleotides

③ – amino acids serine and methionine

- Inhibition of these metabolic processes thereby interferes with the formation of DNA, RNA, and key cellular proteins.

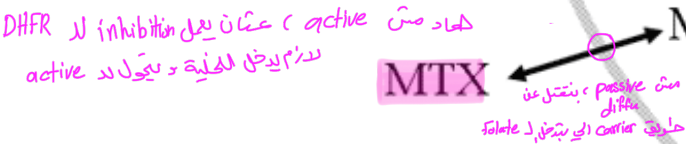
↓ Tetrahydro
بنائز على سبيل المثال ، replication قاع، خلية بنائز ، الباثية عاصية و highly proliferating cells

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*



موجود اصلاً بالخلایا
بیمین polygamete على substrate

الـ intrathecal / IV إذا جاري في السائل
CNS

↓ ⑤
Thymidylate + purine synthesis
↓ ⑥
DNA Synthesis

Methotrexate Resistance

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

(1) decreased drug transport via the reduced folate carrier

بشكل أقل ناقلات ناقصة

(2) decreased formation of cytotoxic MTX polyglutamates,

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

زيادة مستويات DHFR

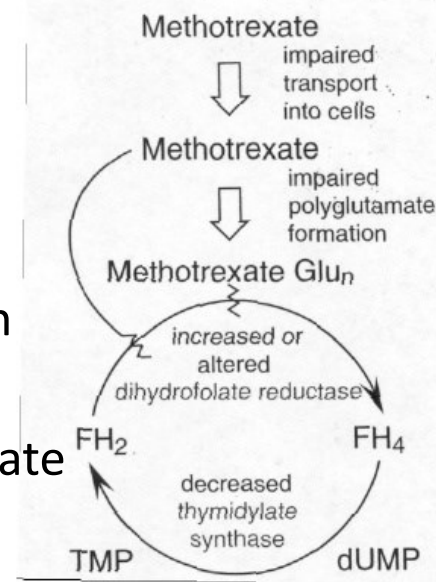
تضخيم الجين المسؤول عن إنتاجه أو طفرات في DHFR تقلل من ارتباطه

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

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

زيادة multidrug resistance gene

تفعيل ناقلات P-glycoprotein التي تخرج الدواء من الخلية

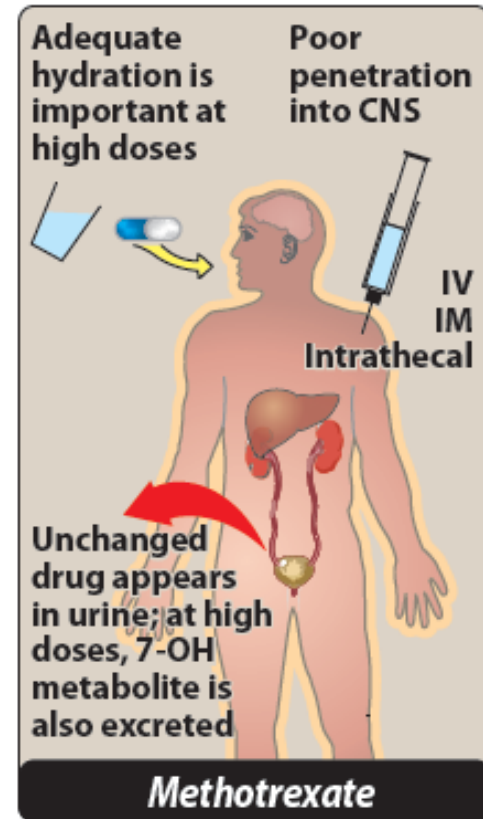


Pharmacokinetics of MTX

- MTX is administered by the ^{إعطاء} ^{الحدود المحدودة} ^{limited dose} 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.

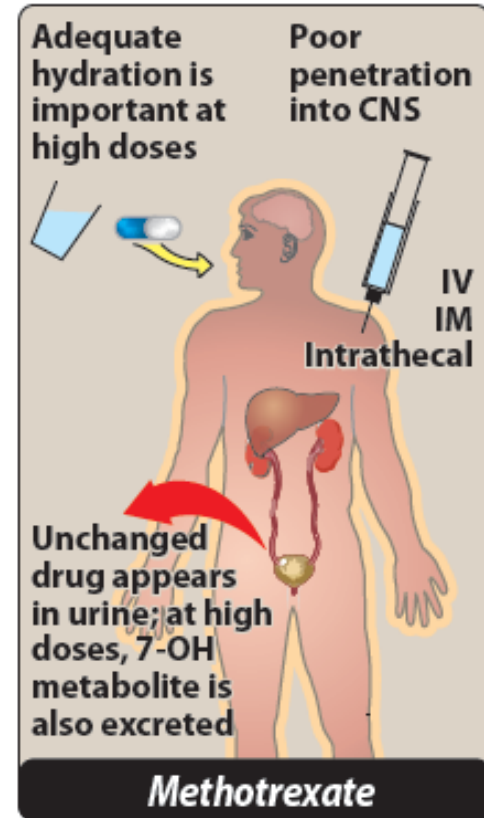
- Care must also be taken when MTX is used in the presence of drugs such as aspirin, nonsteroidal anti-inflammatory agents, penicillins, and cephalosporins, as these agents inhibit the renal excretion of MTX.



جزء unchanged وجزء بهرله metabo
7. position

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**.
علاج با high doses ۱. antiinflammatory ۲. مایع کریستال
- Therefore, it is important to keep the urine alkaline and the patient well hydrated to avoid renal toxicity.



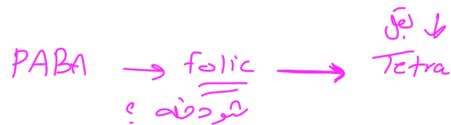
normal cells
high proliferated

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.

* امتنان بعمل جرمين SE يحصلوا مع leucovorin / نقص الـ Folinic acid ^{في Tetra} بعض الاكترى الـ normal cells, Cancer

درجات الـ overdose metho . ليس ما يحلوا folic acid ؟ ما يتغير لانه كبتة بتبقى الـ Tetra من الـ folic acid ^{يقل}



الـ folic ما يتحول الـ Tetra

الي عندهم نقص في الـ folic بوقورا فالك / الـ Cancer الـ Folinic Tetra

Adverse effects of MTX

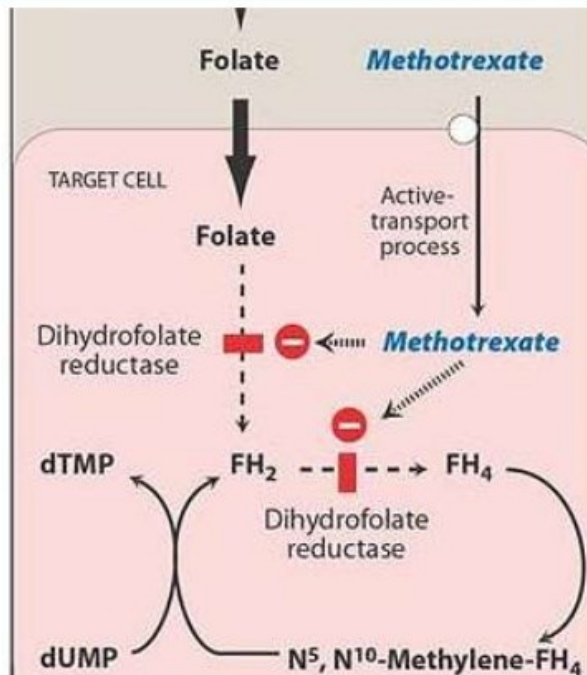
- **Leucovorin** rescue is used in conjunction with high-dose MTX therapy to rescue normal cells from excessive toxicity, and it has also been used in cases of accidental drug overdose.
- However, doses of leucovorin must be kept minimal to avoid possible interference with the antitumor action of MTX.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

* بأثره على الخلايا Cancer لا يتدخل معها metho، أما أسبقنا كميته فغالباً يعطوه الـ folinic في يوم من dose
↓
Cancer cell
يتدخل الـ purine و DNA
الـ metho يكون على مفعول الـ Cancer وليس على الـ normal (لا يتدخل مع الـ cancer أصلاً) (بشكل كبير)

Adverse effects of MTX

Methotrexate

dis



Folic acid not useful in toxicity

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

Adenine, guanine, thymidine, methionine, serine

Methotrexate (MTX)

ال Combination علاج chemo
أكل Dose كل والحدود
دأكل المحافظة

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.

* من كل الالتهاب بجالجوا الادوية / كل دواء الالتهاب

Other Antifolate Drugs

②

1. Pemetrexed

کلاس S

میتو زیاد

- 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).

بازکار
DNA
synthesis

بازکار TS اکثر / باز DHFR بی اثر
main

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 B₁₂ appears to reduce the toxicities associated with pemetrexed, while not interfering with clinical efficacy.

لا يتم التخلص منه بشكل رئيسي من الكلى DHFR

قبل
Pemetrexed

قبل إعطائه Pemetrexed : (premedication) B₁₂

Other Antifolate Drugs

1. Pemetrexed

- The main adverse effects include myelosuppression, skin rash, mucositis, diarrhea, fatigue, and **hand-foot syndrome**. HFS ^{مادة كيميائية}
- 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. ^{يستخدم الستيرويد / HFS / يمكن تقليل الأعراض، يكون}



Other Antifolate Drugs

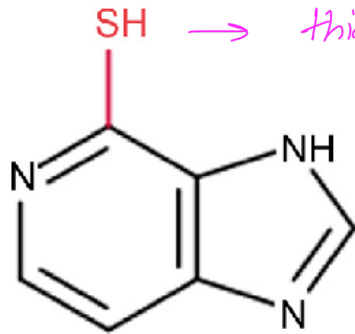
2. Pralatrexate

الاستخدامات غير بـصـاـرـهـنا

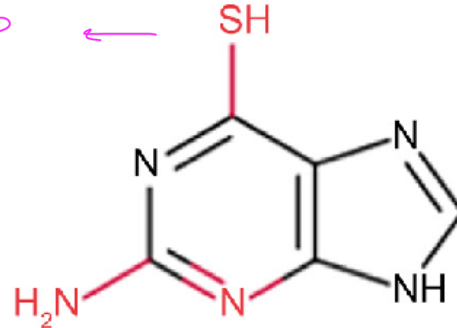
- PK and PD are similar to pemetrexed.
- Does not cause Hand-foot syndrome ما في Corticosteroid
- Vitamin supplementation with folic acid and vitamin B₁₂ appear to reduce the toxicities associated with pralatrexate, while not interfering with clinical efficacy.

Purine antagonists

6-mercaptapurine (thiopurine)



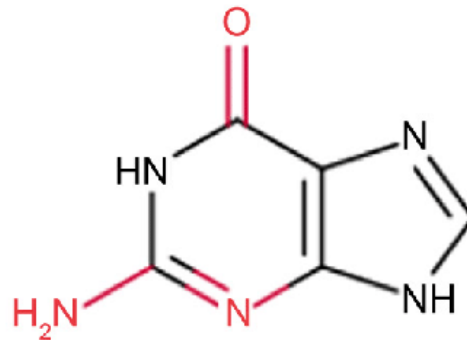
Thioguanine



Adenine



Guanine

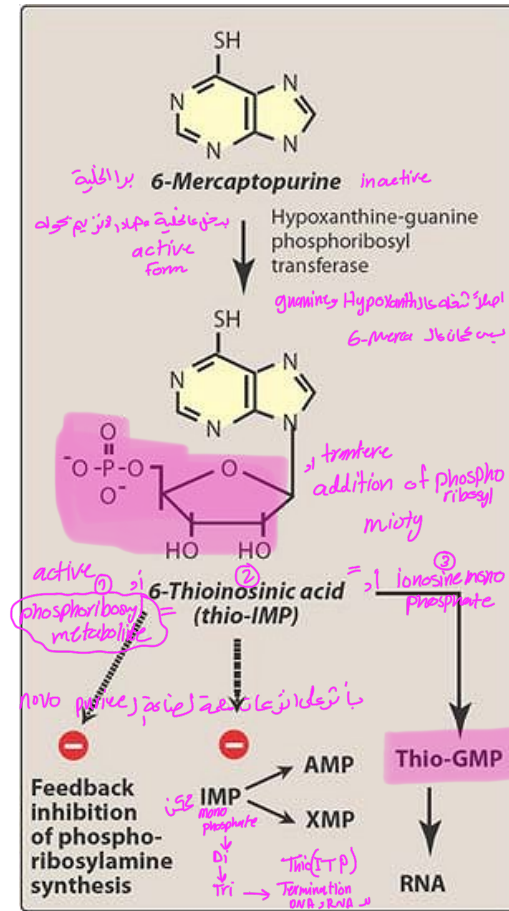


Purine antagonists

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

purine → hypoxanthine → xanthine → uric acid
end product

Resistance:

active لا يتحول إلى منتج نهائي genetic problem

- Decreased levels of HGPRT (for example, in Lesch-Nyhan syndrome) phosphorylated active لا
- Increased dephosphorylation, → active لا يتحول
- Increased metabolism of the drug to (thiouric acid.) inactive
end product of purine

Adverse effects:

- Myelosuppression, immunosuppression, and hepatotoxicity. / bone marrow



liver enzyme ← لا monitoring

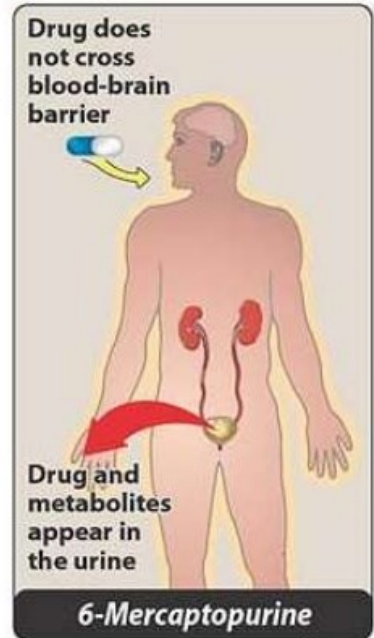
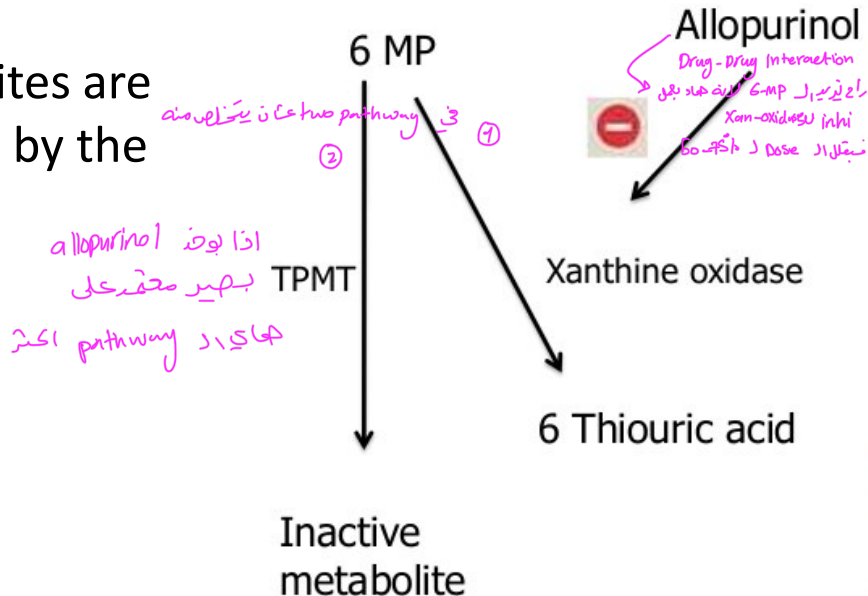
لا يتحول الدواء

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 Mercaptopurine



6-MP

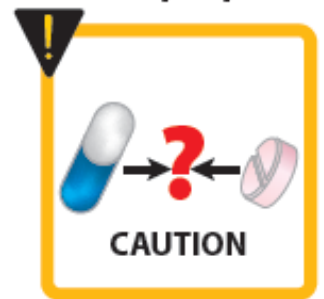
Drug-Drug interactions:

- **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%.

سواء كانت الحالة اذا اجتمعوا
الحوائين بعللوا ال

مرحلة مرض السرطان (Cancer) ينفذوا بكميات كبيرة من Allopurinol حتى لا يرفع مستوى حمض اليوريك في الدم، لأن زيادة حمض اليوريك قد تؤدي إلى الإصابة بمرض النقرس (Gout) الذي يحدث نتيجة لزيادة إنتاج حمض اليوريك (Uric acid) من خلال عملية تسمى lysis. لذلك، يجب تقليل جرعة 6-MP (Mercaptopurine) عند استخدامها مع Allopurinol كإجراء وقائي (prophylactic).

6-Mercaptopurine



Allopurinol

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).

ما دونه
Alo

ميتabolized
بواسطة
deamination

Other Purine Antagonists

Fludarabine

purine synthesis باثردا

- 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.

Funges ↑ T cells
herpes ↑ opportunistic infection [CD4 , CD8] immun cells على كثر باثردا
PCP ↑ فنجوس anti bacteria فنجوس كذاي

trimethoprim مضاداً وسيترايميد العلاج

Other Purine Antagonists

الإنزيمات المثبطة

Cladribine

①
↓ purine
synthesis

②
↓ CD4,8

- 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.

✓
↑ HIV
infection

CoTris

معدول

Done
?

Questions??