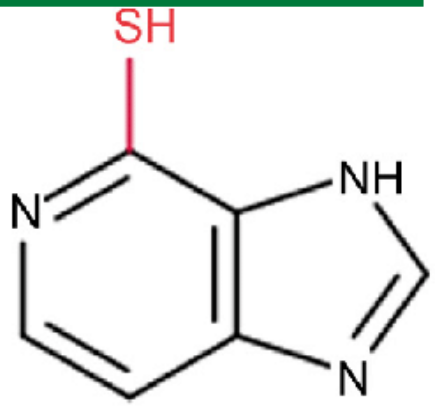
Artery Academy

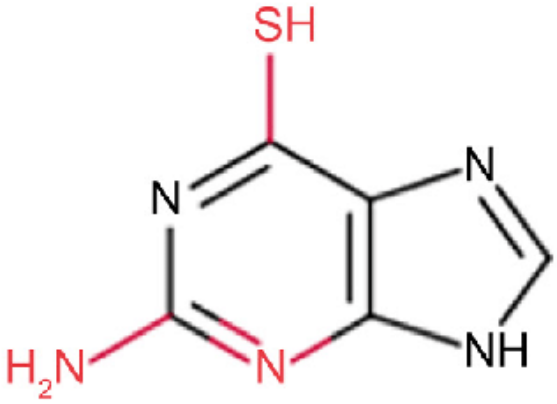
Done By Mariam Yacoub

Purine antagonists

6-mercaptopurine

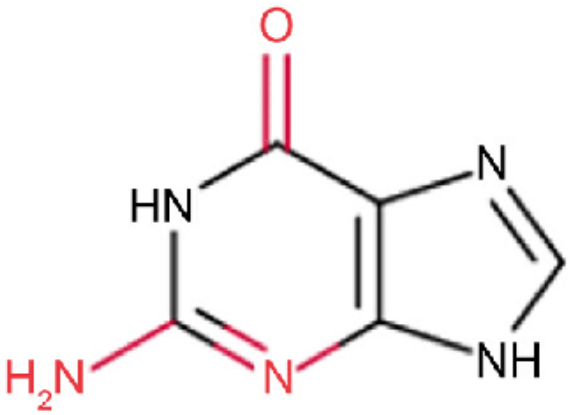


Thioguanine

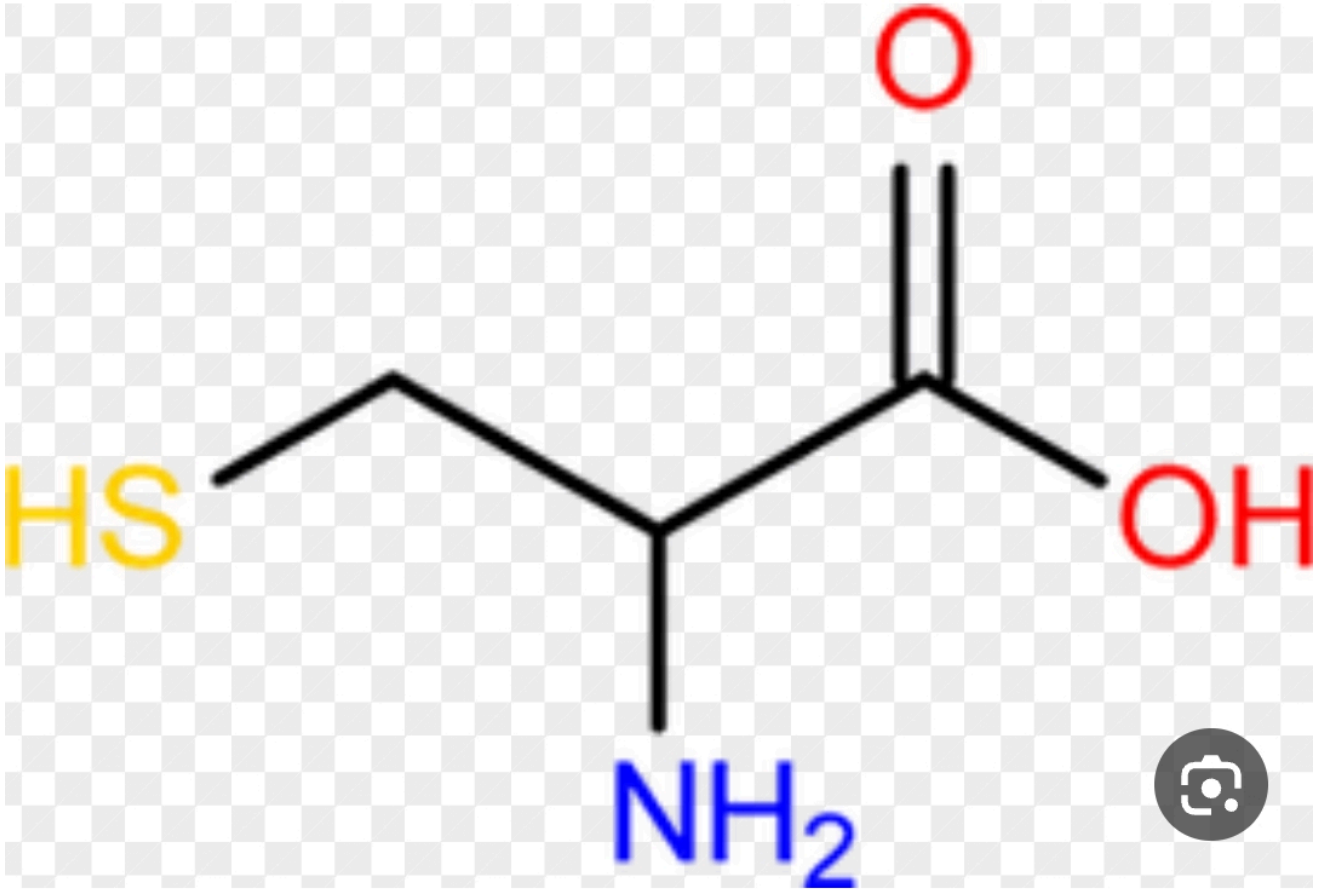


Adenine

Guanine



اختلاف ال 6 **mercaptopurine** عن ال **adenine** هو إنه في **SH group** على بوزيشن ٦ ف بيجي هاد الدوا وبيرتبط بدل ال **adenine** وبثبط تكوين ال **DNA** لل **tumer cells**



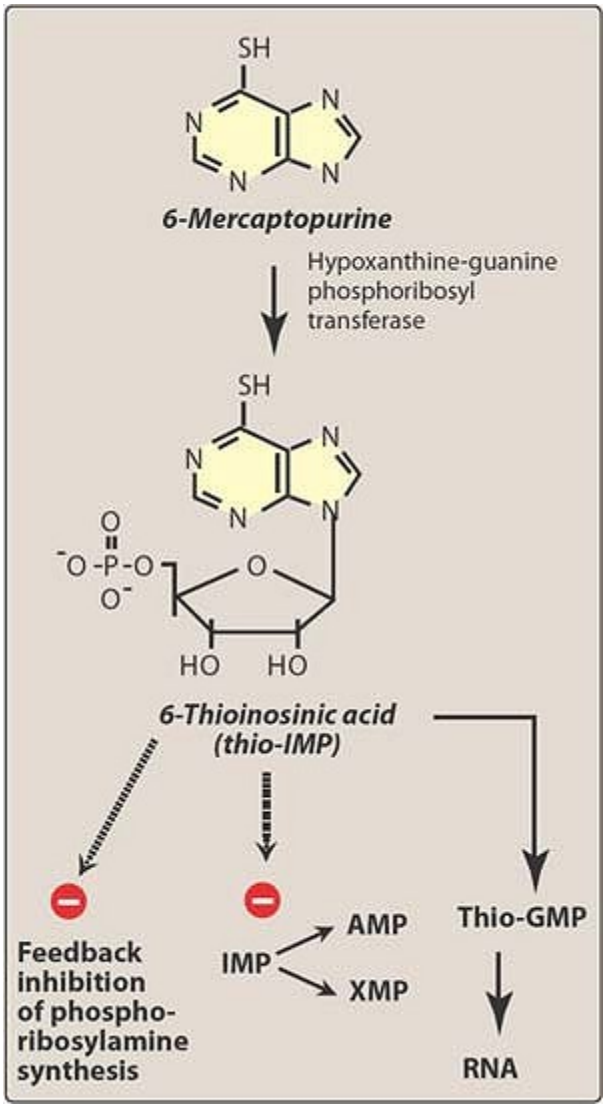
انتقال

What Is a Mercapto Group?

Purine antagonists
6-Mercaptopurine (6-MP)

Mechanism of action:

- **6-Mercaptopurine (6-MP)** was the first of the thiopurine analogs found to be effective in cancer therapy.
- This agent is used in the treatment of AML (acute myelogenous leukemia).
- 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).



يُعتبر ال **mercaptopurine 6** من أول مشتقات ال **thiopurine drug** إلّي تم اكتشاف فعاليتها بعلاج الكانسر
الآن اكتر نوع كانسر بشتغل عليه الدوا هو ال **AML** اختصار ل سرطان الدم النقوي الحاد
هل ح يشتغل ال **mercaptopurine 6** زي ما هو ؟ لا ، بنقدر نعتبره **prodrug** بحيث إنه حيدخل للخليه ويصيرله ميتابوليزم بواسطة ال **HGPRT** ويتحول ل **Thio-IMP** وهاد ال **THio-IMP** رح يشتغل شغله ويعمل تثبيط للإنزيم المسؤول عن تكوين ال **nucleotide**
ومو بس هيك **!**
لا
ح ييجي هاد ال **THio-IMP** وبرضو يصيرله ميتابوليزم تاني ويتحول ل **Triphosphate form** إلّي ح ترتبط ب **DNA+RNA** ما الهم وظيفة

طبعًا أنا كتبت هون بالإختصارات ، ارجعوا للسلايد وشوفوا كل اختصار عبارة عن شو

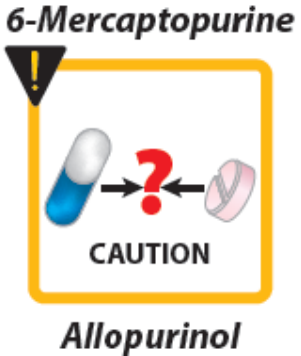
6-MP

Resistance:

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

Pharmacokinetics:

- Absorption by the oral route is erratic and incomplete.
- 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.
- This is an important issue because the purine analog **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%.
- The parent drug and its metabolites are excreted by the kidney.

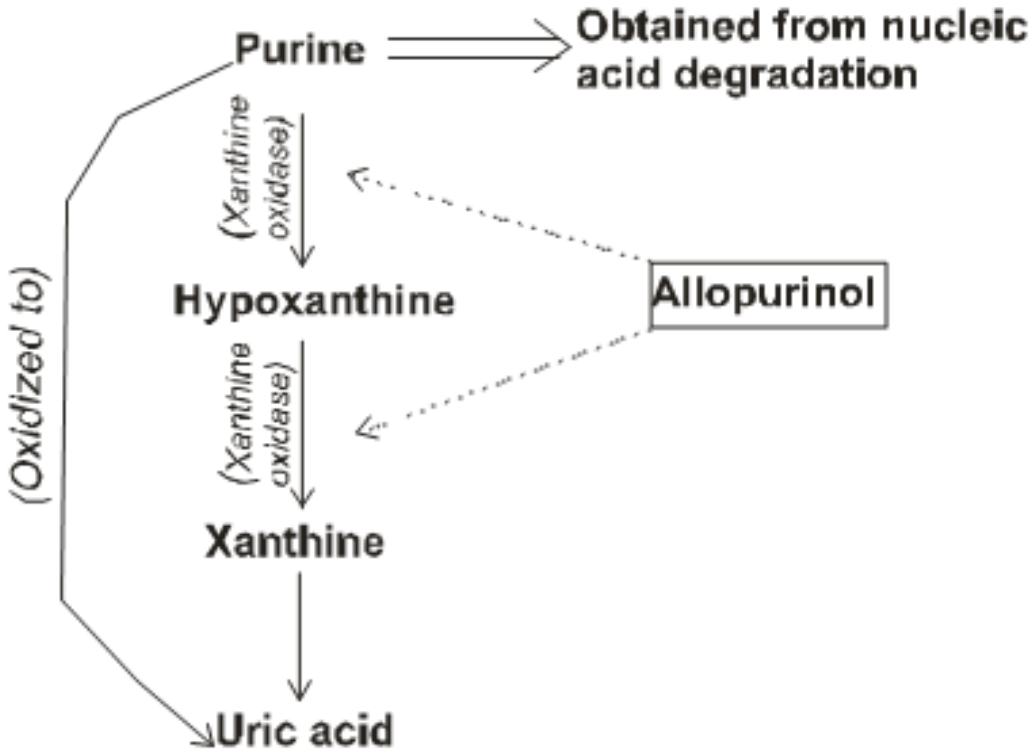


Adverse effects:

- Myelosuppression, immunosuppression, and hepatotoxicity.

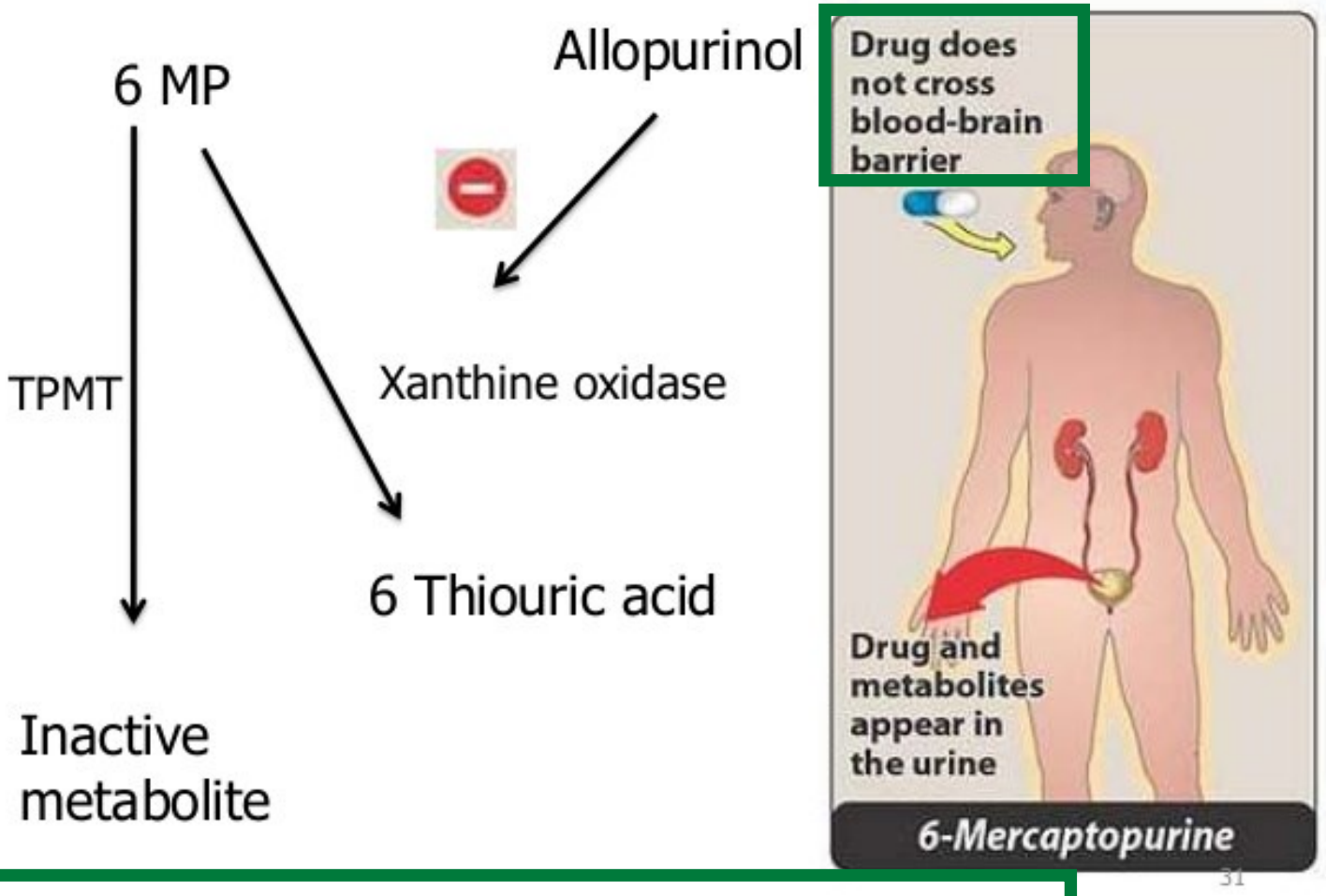
الخلية السرطانية رح تعمل resistance تجاه ال mercaptopurine 6 عن طريقتين :
أول شي بتقلل من تصنيع انزيم HGPRT المسؤول عن تحويل هاد الدوا من ال inactive لل active form ف بالتالي حيضل بال inactive form وما حيأثرلي عالخلية السرطانية وهاي بنسميها lesh-nyhan syndrome
تاني طريقة إني بزيد الميتابوليزم للدوا وبحيث إنه يتحول لل inactive form وهو ال thiouric acid 6 من ناحية PK إعطاءه اورالي حيكون اشي غير منتظم وغير كامل
حكينا حيتحول الدوا هاد mercaptopurine 6 بال liver لل inactive form وهو ال thiouric acid 6 عن طريق إنزيم ال xanthine oxidase وهيك بنتجنب ال toxicity الناتجة من هاد الدوا
هلأ ممكن إني أضطر أجمع بين ال mercaptopurine 6 ومع ال allopurinol إلّي هو يعتبر xanthine oxidase inhibitor متى ؟ وقت يصير tumer cells lysis ونتج عنها hyperuricemia وبعدها بتتطور ل acute leukemia
بس إذا قررت اجمع بينهم حيكون بشرط وهو إني اقلل من جرعة ال mercaptopurine 6 ل ٥٠ او ٧٥٪
ليش ؟ عشان ال mercaptopurine 6 هون ما حيكون قادر يتحول لل inactive form ف بالتالي ممكن يصير toxicity
بالنهاية كل ال mercaptopurine 6 والأشياء ألّي نتجت منه ح تطلع بال kidney

اخر شي ال adverse effects ححط عليهم هايلايتر
بالنهاية أنا بقدر اجمع بين ال mercaptopurine 6 وال allopurinol بس بشرط تقليل الجرعة ✅



Mechanism of Action of Allopurinol
(Jeepakistan.blogspot.com)

6 Mercaptopurine



When allopurinol is given with 6-MP, the dose of mercaptopurine must be reduced by 50–75%.

Other Purine Antagonists

6-Thioguanine (6-TG)

نفس ال **mercaptopurine 6** بثبط الإنزيمات المسؤولة عن تكوين ال **nucleotide**

- **6-TG** also inhibits several enzymes in the de novo purine nucleotide biosynthetic pathway.
- 6-TG has a synergistic action when used together with cytarabine in the treatment of adult acute leukemia.

استخدامه مع ال **cytarabine**
بعلاج ال **acute leukemia**

- 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).

بصيرله ميتابوليزم عن طريق ال **deamination** مش ال **oxidation** ف بالتالي ما
حيتأثر بال **allopurinol** وبعطي جرعته كاملة عادي
من ناحية **side effects** ف نفس ال **mercaptopurine 6**

Other Purine Antagonists

Fludarabine

- This purine nucleotide analog is used mainly in the treatment of low-grade non-Hodgkin's lymphoma and chronic lymphocytic leukemia (CLL).
- It is given parenterally, and up to 25–30% of parent drug is excreted in the urine.
- 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.

بالنسبة للـ Fludarabine يُعتبر من ال purine analog إلّي ح يثبط من تشكيل ال nucleotide
بشتغل على أنواع معينة من الكانسر ححط عليها هايلايتر
بينعطى parenteral و فقط ٢٥-٣٠٪ بصيرلها excretion in the urine
الشي إلّي بسببه وبخلينا ننتبه بتحديد الجرعة لحتى نتجنب ال toxicity هو ال myelosuppressant
بيعمل inhibition لشو ؟ لل CD4 and CD8 T cell وبعمل immunosuppressant
وبزيد خطر الإصابة بالأمراض الإنتهازية سواء فيروسات او فطريات او غيره وبالذات ال PCP
لهيك أي مريض بياخد ال Fludarabine بعد ما يوقف الدوا لازم يمشي ع علاج ال trimethoprim-sulfamethoxazole تلات مرات أسبوعيا على الأقل ولمدة سنة

Other Purine Antagonists

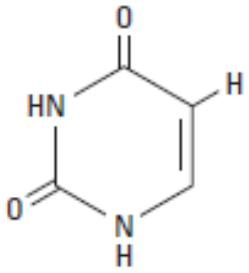
Cladribine

أنواع الكانسر إلّي بشتغل عليها :

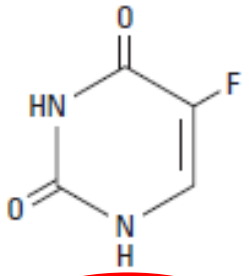
- Cladribine is indicated for the treatment of hairy cell leukemia, with activity in other low-grade lymphoid malignancies such as CLL and low-grade non-Hodgkin's lymphoma.
- It is normally administered as a single continuous 7-day infusion; under these conditions, it has a very manageable safety profile 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.

بنعطى بجرعة وحدة متواصلة لمدة أسبوع ولازم خلال هالفترة نراقب ال **myelosuppressant**
يجماعة رَيحوا حالكم واربطوا ال **purine antagonist= myelosuppressant**
ونفس إلّي قبل من ناحية تأثيره على ال **immunosuppressant** وال **CD4 and CD8 T cell** ولازم
المريض يستمر عالعلاج لمدة سنة عالأقل

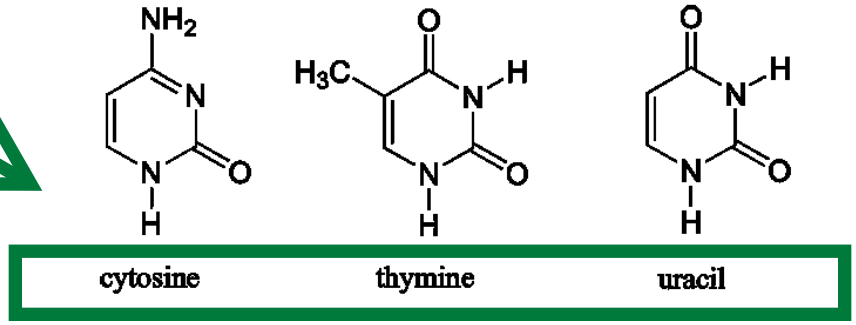
Pyrimidine antagonists



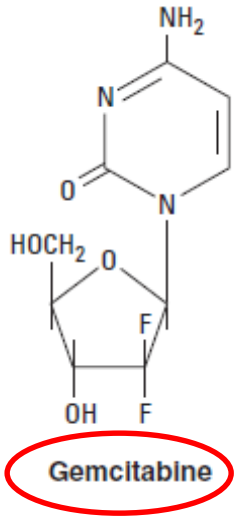
Uracil



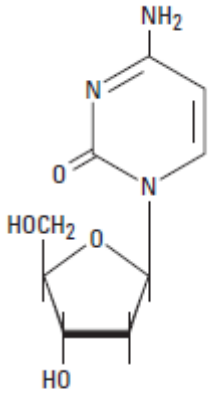
5-FU



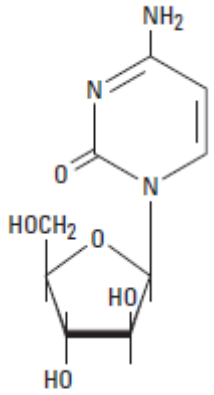
ضفنا فلور على بوزيشن ٥
من ستركشر ال **uracil** ف
نتج عنه **5flurouracil**



Gemcitabine



Cytosine deoxyriboside



Cytosine arabinoside (cytarabine)

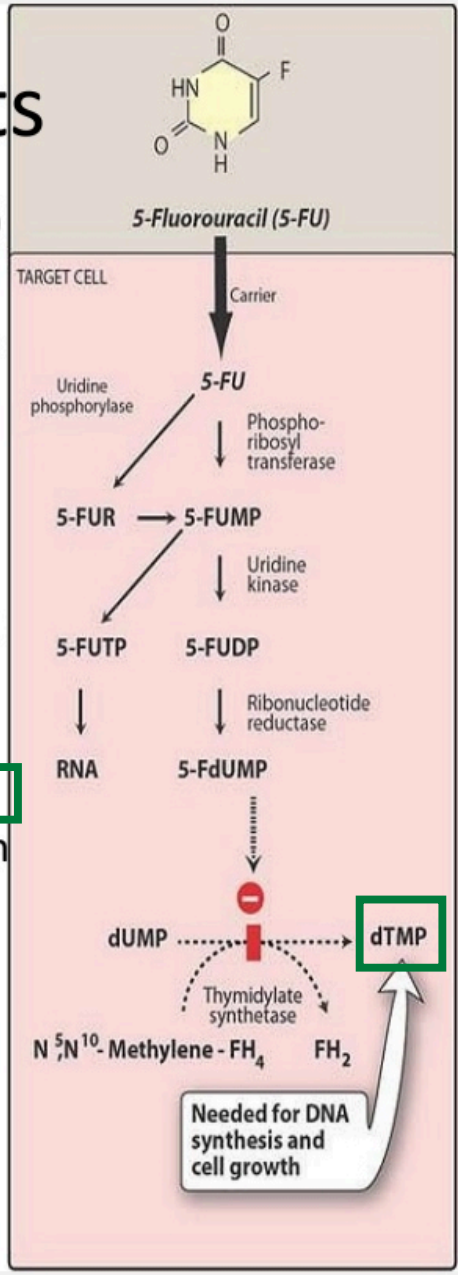
Pyrimidine antagonists
5-Fluorouracil (5-FU)

Mechanism of action:

- 5-Fluorouracil (5-FU) is inactive in its parent form and requires activation via a complex series of enzymatic reactions to ribosyl and deoxyribosyl nucleotide metabolites. One of these metabolites, 5-fluoro-2'-deoxyuridine-5'-monophosphate **(FdUMP).**

1. FdUMP inhibits the enzyme thymidylate synthase (TS) which mediate a reaction critical for the de novo synthesis of thymidylate.
2. 5-FU is converted to 5-fluorouridine-5'-triphosphate **(FUTP),** which is then incorporated into RNA, where it interferes with RNA processing and mRNA translation.
3. 5-FU is also converted to 5-fluorodeoxyuridine-5'-triphosphate **(FdUTP),** which can be incorporated into cellular DNA, resulting in inhibition of DNA synthesis and function.

- Thus, the cytotoxicity of 5-FU is thought to be the result of combined effects on both DNA- and RNA-mediated events.



هاد ال FU-5 بنقدر نعتبره as pro drug عن طريق مجموعة من ال enzymatic activation ح يتحول لل active form
لشو رح يتحول ؟ ل ribosyl and deoxyribosyl nucleotide
مثال عليهم ال FdUMP ارجعوا للسلايد لحتى تعرفوا اختصار لشو ، المهم هاد الجزء رح يثبط عمل ال Thymidylate synthase المسؤول عن تشكيل أصلاً ال Thymidylate
وكمان هاد ال FU-5 رح يتحول ل FUTP المسؤول على إنه يرتبط بال mRNA ويثبط عملها
وكمان رح يتحول ل FdUTP إلّي ح يرتبط بال DNA ويثبط تكوينه ووظيفته
يعني هاي ال FU-5 تحولت لتلات أشكال وكل شكل اشتغل ع شي
ف بستنتج إنه هاد ال FU-5 أعطاني combination effects على ال DNA and RNA

5-FU

بستخدمه بشكل أساسي لعلاج ال **colorectal cancer** وممكن
استخدمه بعلاج ال **solid tumer** رح احط تحتهم خط

Clinical uses:

- 5-FU remains the most widely used agent in the treatment of colorectal cancer, both as adjuvant therapy and for advanced disease.
- It also has activity against a wide variety of solid tumors, including cancers of the breast, stomach, pancreas, esophagus, liver, head and neck, and anus.

ممكن أستخدمه ك علاج مساند مع
علاجات تانية أو لعلاج مرض متقدم

Side Effects:

- Major toxicities include:

1. Myelosuppression
2. Gastrointestinal toxicity in the form of mucositis and diarrhea
3. Skin toxicity manifested by the hand-foot syndrome
4. Neurotoxicity.

من أهم أعراضه الجانبية على ال **GI , Skin, Neurons**, وأهم شي ال
hand-foot syndrome إلّي حكينا عنها بال **pemetrexed** وكانت من
أعراضها **painful erythema and swelling of the hands and feet**

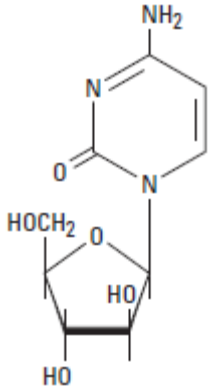
5-FU

Pharmacokinetics:

- 5-FU is administered intravenously. Because of its extremely short half-life, on the order of 10–15 minutes, infusional schedules of administration have been generally favored over bolus schedules.
- Up to 80–85% of an administered dose of 5-FU is **catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD).** Of note, a pharmacogenetic syndrome involving partial or complete deficiency of the DPD enzyme is seen in up to 5% of cancer patients. In this particular setting, severe toxicity in the form of myelosuppression, diarrhea, nausea and vomiting, and neurotoxicity is observed.
- Although mutations in DPD can be identified in peripheral blood mononuclear cells, nearly 50% of patients who exhibit severe 5-FU toxicity do not have a defined mutation in the *DPD* gene. In addition, such mutations may not result in reduced expression of the DPD protein or in altered enzymatic activity. For this reason, genetic testing is not recommended at this time as part of routine clinical practice.

ال FU-5 بينعطى IV ليش ؟ لإنه عنده short half life وبفضل وقت أعطيه أستخدم ال infusion أكتر من ال bolus schedules
تقريبًا ٨٠ ل ٨٥٪ من الجرعة حيصيرلها catabolized بواسطة إنزيم DPD وجدوا إنه تقريبًا ٥٪ من مرضى الكانسر عندهم نقص جزئي أو كلي لهاد الإنزيم ، تلقائيًا بتوقع طالما صار في نقص بالإنزيم المسؤول عن ال catabolized للدوا ف بالتالي حيتراكم الدوا وأشوف ال toxicity إله ع شكل myelosuppression, diarrhea, nausea and vomiting, and neurotoxicity
كيف ممكن أكشف ع وجود mutation بهاد الإنزيم ؟ عن طريق blood mononuclear cells بس في شغلة مهمة وهي إنه مو شرط دايمًا المشكلة تكون mutation أو نقص ، ممكن تكون بسبب reduced expression of DPD أو alteration in enzyme activity وهاد الإشي وجدوه عند تقريبًا ٥٠٪ من مرضى الكانسر
الأهم من هاد كله إني أحاول أتجنب ال genetic testing لإنه لا يُفضل بال clinical practice

Other pyrimidine antagonists
Cytarabine



Cytosine arabinoside (cytarabine)

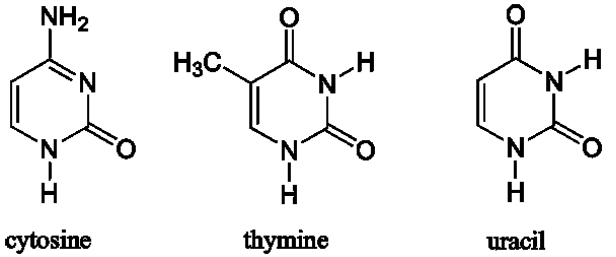
Mechanism of action:

- **Cytarabine (ara-C)** is converted by deoxycytidine kinase to the 5'-mononucleotide (ara-CMP). Ara-CMP is further metabolized to the diphosphate and triphosphate metabolites, **ara-CTP is the main cytotoxic metabolite**.
- Ara-CTP:

1. competitively inhibits DNA polymerase-α and DNA polymerase-β, thereby resulting in blockade of DNA synthesis and DNA repair, respectively.
2. is also incorporated into RNA and DNA. Incorporation into DNA leads to interference with chain elongation.

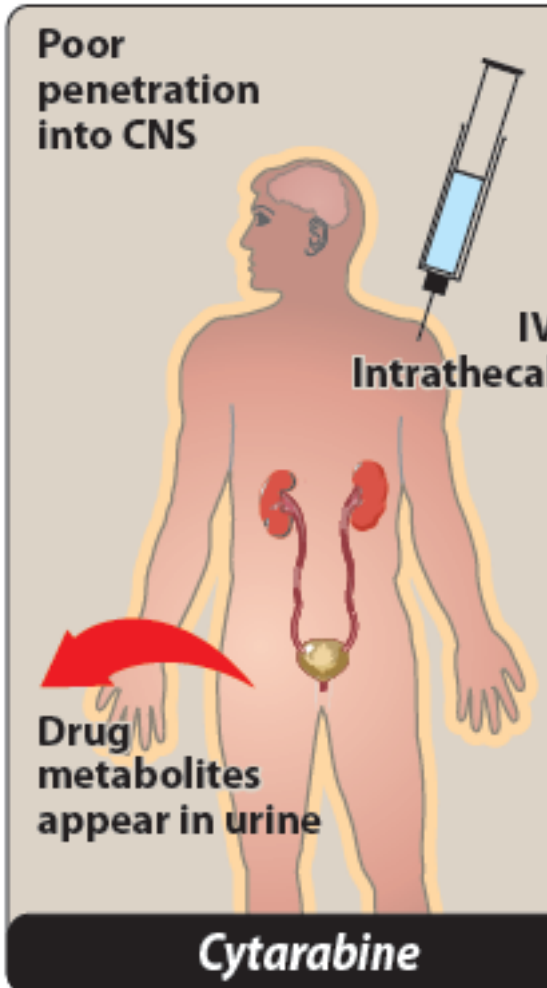
هاد ال **cytarabine** برضو بنعتبره **prodrug** بيتحول عن كريق ال
deoxycytidine kinase ل **mononucleotide-5** وهاد ال **mono** بكمل
الميتابوليزم وبتحول ل **di** وبعدها **tri** لكن اهم اشي بال **cytotoxic metabolites**
هو ال **ara-CTP**
بيشتغل عن طريق إنه بيعمل **inhibition** لل **DNA polymerase alpha and**
beta ف بالتالي ح يصير في **blockage** لتكوين وال **repair** لل **DNA**
وممكن يرتبط بال **DNA, RNA** ويوقف السلسلة

Other pyrimidine antagonists
Cytarabine



Pharmacokinetics:

- *Ara-C* is not effective when given orally, because of its deamination to the noncytotoxic ara-U by cytidine deaminase in the intestinal mucosa and liver.
- Given IV, it distributes throughout the body but does not penetrate the CNS in sufficient amounts to be effective against meningeal leukemia. However, it may be injected intrathecally.
- *Ara-C* undergoes extensive oxidative deamination in the body to ara-U, a pharmacologically inactive metabolite. Both *ara-C* and ara-U are excreted in urine.



Other pyrimidine antagonists
Cytarabine

Clinical uses:

- The clinical activity of cytarabine is highly schedule-dependent and because of its rapid degradation, it is usually administered via continuous infusion over a 5–7 day period.
- Its activity is limited exclusively to hematologic malignancies, including acute myelogenous leukemia and non-Hodgkin's lymphoma.
- This agent has absolutely no activity in solid tumors.

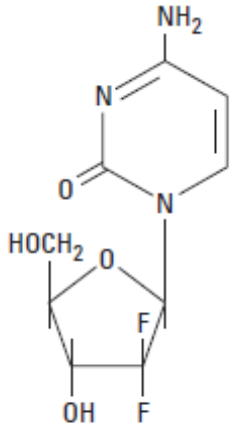
نركز هون إنه هو الوحيد بهاد الچروب ما حيتشغل عال **solid tumer**

Side Effects:

- The main adverse effects associated with cytarabine therapy include myelosuppression, mucositis, nausea and vomiting, and neurotoxicity when high-dose therapy is administered.

ال **neurotoxicity** هون بتصير عند الجرعات العالية منه

Other pyrimidine antagonists
Gemcitabine



Gemcitabine

Mechanism of action:

- **Gemcitabine** is a fluorine-substituted deoxycytidine analog that is phosphorylated initially by the enzyme deoxycytidine kinase to the monophosphate form and then by other nucleoside kinases to the diphosphate and triphosphate nucleotide forms.
- The antitumor effect is considered to result from several mechanisms:

1. inhibition by gemcitabine triphosphate of DNA polymerase-α and DNA polymerase-β, thereby resulting in blockade of DNA synthesis and DNA repair
2. incorporation of gemcitabine triphosphate into DNA, resulting in chain termination.
3. inhibition of ribonucleotide reductase by gemcitabine diphosphate, which reduces the level of deoxyribonucleoside triphosphates required for DNA synthesis

بالنسبة لل gemcitabine يُعتبر deoxycytidine analog بس عليه فلورايد
حيصيرله فسفرة عن طريق انزيم ال deoxycytidine kinase ويتحول ل.
monophosphate وبعدها بتحول ل di وبعدها ل Triphosphate
كيف حيشتغل ك دوا بعلاج السرطان ؟
نفس الميكانزيم الأولى والتانية مشتركة مع ال cytarabine
بس حنضيف عليهم تالت ميكانيزم وهي إنه رح يعمل inhibition of
ribonucleotide عن طريق ال gemcitabine diphosphate ف بالتالي ما
حيقدر يتحول لل Triphosphate وإلّي بحتاجه بتصنيع ال DNA

Other pyrimidine antagonists
Gemcitabine

Clinical uses:

- In contrast to cytarabine, which is inactive in solid tumors, **gemcitabine** has broad-spectrum activity against solid tumors and hematologic malignancies. This nucleoside analog was initially approved for use in advanced pancreatic cancer but is now widely used to treat a broad range of malignancies, including NSCLC, bladder cancer, ovarian cancer, soft tissue sarcoma, and non-Hodgkin's lymphoma.

Side Effects:

1. Myelosuppression in the form of neutropenia is the principal dose-limiting toxicity.
2. Nausea and vomiting occur in 70% of patients
3. a flu-like syndrome has also been observed.

بنستخدم ال gemcitabine بعلاج ال solid tumer
نتذكر سوا شو كانوا ال solid tumer? breast, stomach, pancreas, esophagus, liver, head and neck, and anus.
يعني بنقدر نحكي إنه الوحيد من ال pyrimidine antagonist إلّي ما بيشتغل على ال solid tumer هو ال Cytarabine
نرجع لل gemcitabine ح يشتغل كمان على مجموعة واسعة من الكانسر ححط عليهم هايلايتر

من أهم أعراضه الجانبية هي ال myelosuppressant المشتركة بينهم كلهم
وكمان ٧٠٪ من المرضى الكانسر إلّي بياخدوا هاد العلاج بصير معهم nausea and vomiting and flu like syndrome

Questions?? No 🌚

خلصنا!!!! 💚

لهون بتكون نهاية مادة السكند