Pyrimidine antagonists

Fluorouracil (5-FU)

- 5-FU is incorporated into both RNA and DNA.

5-FU is converted to 5-FdUMP, which competes with deoxyuridine monophosphate (dUMP) for the enzyme thymidylate synthetase.

5-FU = 5-fluorouracil

5-FUR = 5-fluorouridine

5-FUMP = 5-fluorouridine monophosphate

5-FUDP = 5-fluorouridine diphosphate

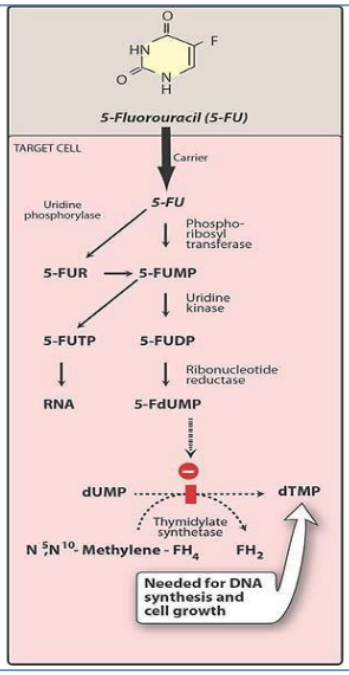
5-FUTP = 5-fluorouridine triphosphate

dUMP = deoxyuridine monophosphated

TMP = deoxythymidine monophosphate

5-FdUMP = 5-fluorodeoxyuridine monophosphate.

- *Leucovorin* is administered with *5-FU,* because the reduced folate coenzyme is required in the thymidylate synthase inhibition



Pyrimidine antagonist they look like pyrimidine base

طبعا غير الpurine حكينا عن ال MP like similar almost look thioguanine لكن بعض ال adverse reaction and drug- drug interaction are less to be seen with thioguanine مقارنة بال 6-MP

5-FU طبعا تفاصيل الرسمة والاختصارات مش مطلوبة

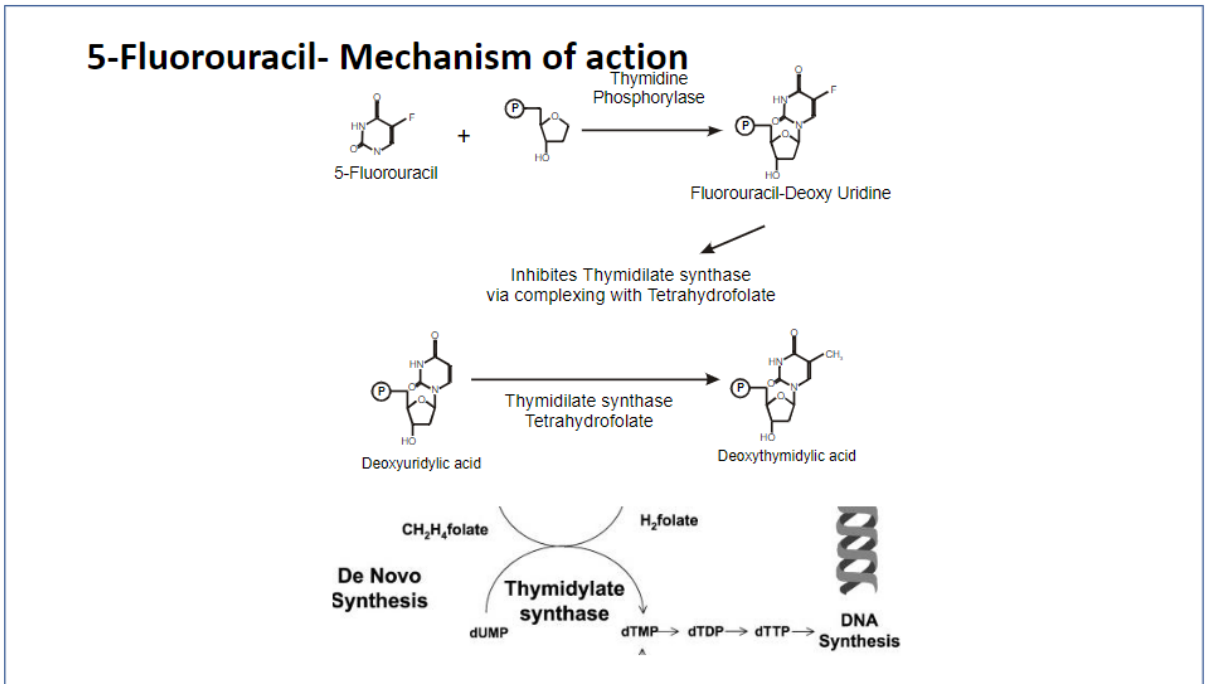
5-FU بدخل الtarget cell من البداية طبعا من خلال career بعدها بصير اله فسفرة phosphoribosyl transferase enzyme المهم اخر اشي هوه المهم ال 5-FU في الشكل الطبيعي رح يتحول من dump الى dtmp

Thymidine bases ready to be corroborated in the DNA synthases

duMP هذا المركب رح يعمل inhibition for thymidylate synthetase كون عملتله 5-FU you will block the synthesis of the thymidine باستخدام ال inhibition which is needed for replication and cell growth so when we cancel this step we will induce cell death and impair the DNA replication in that cell

وجدوا انه هذا الانزيم اللي بعمل inhibition بساعد further to get a powerful inhibition of 5-FU this is has been done if 5-fu administered with leucovorin or in reduced form of folic acid will enhance the inhibition of thymidylate synthetase by 5-fu

معناها كل ما اعطي ال leucovorin to control methotrexate adverse reaction wile leucovorin given with 5-FU to enhance anti-cancer action to enhance the inhibition thymidylate synthetase هوة بشتغل لحاله بس انت بدك تحسن ال action

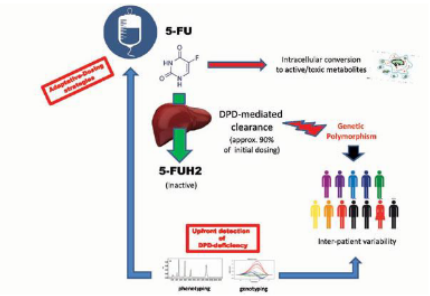


حكت الدكتورة المخطط سريع

Pyrimidine analoges-Fluorouracil (5-FU)

- 5-FU is administered intravenously b/c of its severe toxicity to the GIT.
- The dose of *5-FU* must be adjusted in impaired hepatic function.
- Elevated levels of dihydropyrimidine dehydrogenase (DPD)

can increase the rate of *5-FU* catabolism and decrease its bioavailability. The DPD level varies from individual to individual.



- complete deficiency ofthe DPDenzyme 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 isobserved.

هذا الدوا منيح وموجود في بروتوكولات for breast or colorectal

اله مشاكل ما بنعطي oral لأنه اله local GI toxicityوهوه بصير اله ميتابولزم في الكبد عشان هيك لازم نعدل الجرعة في حالات ال hepatic impairment

الميتابولزم اله under genetic controlبتحكم في جين معناها هوه under polymorph في ناس بتسرع وناس بتبطا عشان الانزيم اللي بتحكم فيه DPD

احنا بنعمل للمريض قبل ما ياخد أي علاج كيماوي GENERAL VISTEGATION

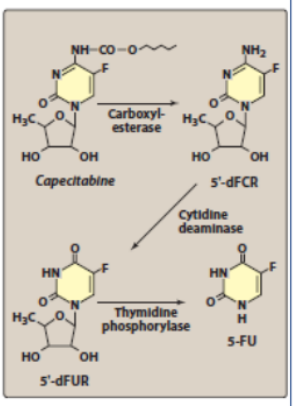
مثل cbc نعرف ال bone marrow action بنعمله hepatica function بدنا نشوف انزيمات الكبد بس في تفاصيل ما بتبين في الفحوصات العادية اللي هيه ال polymorphism

ال 5-FU في ناس بصير عندهم toxicity

Pyrimidine antagonists-Capecitabine

- oral fluoropyrimidine carbamate.
- undergoes a series of enzymatic reactions, the last of which is hydrolysis to *5-FU*. This step is catalyzed by thymidine phosphorylase, an enzyme that is concentrated primarily in tumors.
- Main toxicities of capecitabine include diarrhea and the hand-foot syndrome.

While myelosuppression, nausea and vomiting, mucositis, and alopecia are also observed with capecitabine, their incidence is significantly less than that observed with intravenous 5-FU.



في دوا بتحول داخل الخلية لـ5-FU يعني بدنا نحكي pro drug اللي هوه ال capecitabine

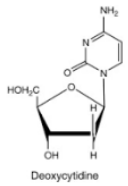
وبنعطي oral وبتحول ل 5-FU في الخلية ونفس الشي بكمل ال actionنفس ما حكينا قبل

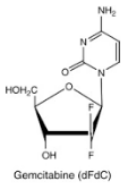
لكن للأسف الله مشاكل gastrointestinalاكثر من ال 5FU- بالإضافة ل hand-foot syndrome بصير عند الناس اللي بياخدوا تغير في لون اليد او الاضافرممكن يفقد الإحساس

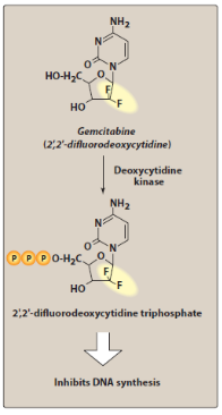
Pyrimidine antagonists-Gemcitabine

- Is an analog of the nucleoside deoxycytidine
- Is a substrate for deoxycytidine kinase, which phosphorylates the drug to 2′,2′-difluorodeoxycytidine triphosphate.
- *Gemcitabine* is infused IV.

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







بشبه ال deoxycytidine اللي بتحول ل cytosine الاختلاف بس بالفلور

بدنا نعرف انه حصول ال activation by kinase enzyme become active it finally inhibited DNA بنحكي ليش في ادوية كتيرة بس لانهم وجدوا انه كل دوا اله خصوصية معينة على نوع معين من السرطان

هاي ال neutropenia ممكن تؤدي can induce fever du to infection and the patient because of the drop in the neutrophil count (they have a rule as defense mechanism) so its conceded a dose limiting toxicity that should be taken in consideration once its develop you can not increase the dose and sometime we make withdrawal to use other medication

احنا بنخاف من ال fever بسبب نقصان عدد ال neutrophils

MICROTUBULE INHIBITORS-Plant alkaloids

- These classes differ in their structures and MOA but share the multidrug resistance mechanism.
- **Cell cycle specific agents**
  - Vinca alkaloids (vinblastine, vincristine)
  - Taxanes (paclitaxel, docetaxel)

خلصنا من ال S phase هسا بدنا نروح لل G2 phase

ممكن ال antimetabolite تأثر على ال G2 لأنه بدايته الDNA بدها تدخل الخلايا بتصنيع البروتينات اللي بتحتاجها لل mitosis ووجود ال DNA هوه اللي بتحكم بتصنيع البروتين وتكرار الخلايا هسا بدها تدخل الخلية بال M phase اللي هوه ال mitosis واهم اشي بالانقسام هيه ال microtubules (الخيوط المغزلية) اللي بتسحب الكروموسومات لأقطاب الخلية وبتكون جاهزة للانقسام حتى نحصل على خليتين من وحدة

في anti-cancer بتأثر على ال microtubules and they will empire cell division so it cell cycle specific affecting M phase

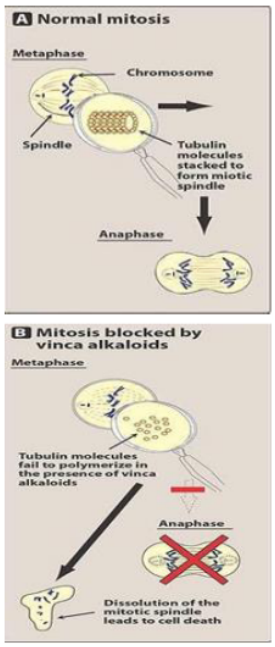
Vinca alkaloid and it start prefixes Vin

Taxine end with suffix taxel

التنين باثروا على ال microtubules but in different action

Vinca alkaloids: Vinblastine, Vincristrine

- Structurally related compounds derived from *Vinca rosea* (Vinblastine & vincristrine).
- Despite their structural similarity, there are significant differences between them in regard to clinical usefulness and toxicity.
- **MOA:** The vinca alkaloids bind avidly to tubulin & inhibition tubulin polymerization, which disrupts assembly of microtubules. This inhibitory effect results in mitotic arrest in metaphase (M) prevent, and cell division cannot be completed



اول ما تبدا بدها تصير عملية انقسام الخلية رح يصير تكوين للخيوط المغزلية التكوين هذا احنا بنسميه assembly or polymerization هذا بصير اله inhibition with vinca alkaloids احنا بنمنعها , بالوضع الطبيعي بتتكون ال tubulins وبصير الها polymerization وبتكون ال bundles وبتدخل الخلية بطور ال anaphase وبتكون الخلايا او الخيوط المغزلية جاهزة تسحب الكروموسومات وبصير الانقسام لكن اذا استخدمنا ال vinca alkaloid ما بصير تكون او polymerization لل tubulin وبالتالي الخلية بتضل ثابتة على ال M phase لانهم افي خيوط مغزلية اللي تمسك الكروموسوم وتبدا تسحب في هون الخلية بتكون unstable this will cause dissolution of microtic spindle this will cause or induce cell death وهذا جيد وتعتبر هذه الادوية فعاليتها عالية ف انقسام الخلية بكون غير كامل والخلية بتموت هيه صح cell cycle specific but they will effect both cancer as will as highly divided cell

Vinca alkaloids: Vinblastine, Vincristrine

- **Pharmacokinetics :**
- Intravenous injection leads to rapid cytotoxic effects and cell destruction.
- The vinca alkaloids are concentrated and metabolized in the liver by the cytochrome P450 pathway. They are excreted into bile and feces.

- **ADRs**

Vinblastine:

- NV, **bone marrow suppression**, alopecia.

Vincristine:

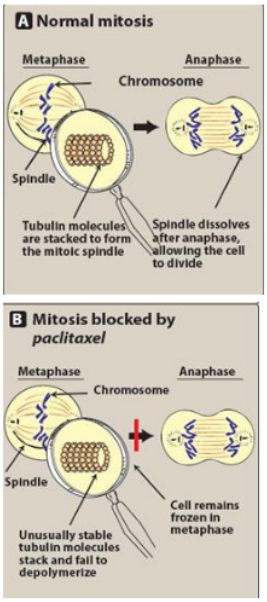
- **Neurotoxicity**: peripheral sensory neuropathy
- Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

عدا عن ال general ADRs فهي بتتميز high myelosuppression

اما ال vincristine اله neurotoxicity عالية حتى ال autonomic nerve also effected وبنتوقع يزيد ال fluid retention الانه ما في urination

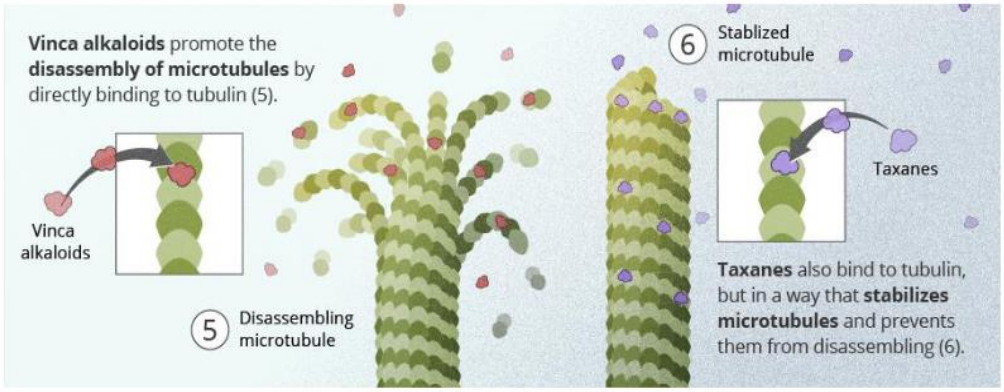
Taxanes: Paclitaxel, Docetaxel

- **Cell cycle specific (G2/M phase of the cell cycle)**
- **MOA**: They bind reversibly to the β-tubulin subunit promoting polymerization and stabilization of the polymer rather than disassembly. Thus, they shift the depolymerization-polymerization process to accumulation of microtubules. The overly stable microtubules formed are nonfunctional, and chromosome desegregation does not occur. This results in death of the cell



الشكل التاني بس تحديدا بتأثر على M phase هون العكس احنا حكينا ال tubule لما يصير الها formation بصير الانقسام وبتسحب الكروموسوم وخلص لكن المشكلة انه بس يتكون

الكروموسومات لازم تتحلل ما بتضل موجودة هسا ال depolymerization لهاي ال microtubules is inhibited by taxanes يعني يا اما بناثر على ال formation من خلال ال alkaloid او بناثر على ال depolymerization من خلال ال taxane



شرحت الدكتورة وحكت عن الصورة

Taxanes: Paclitaxel, Docetaxel

- **ADRs:**
  - **Neutropenia:** treatment with colony stimulating factor (Filgrastim) can help
  - **Peripheral neuropathy**
  - **Transient, asymptomatic bradycardia:** Paclitaxel
  - **Fluid retention:** Docetaxel
  - **Serious hypersensitivty:** patients are pre-treated with dexamethazone, diphenylhydramine.

حكت الدكتورة عن النقطة الأولى وأنها تعتبر dose limiting

دائما المريض بياخد العلاج ولازم بعدها يرتاح بنعطي مجال للخلايا الطبيعية حتى تعمل regenerate سواء الشعر او خلايا المبطنة للمعدة وبكون عنده فرصة كبيرة وعرضة لل infection

Antitumor antibiotics

- Antitumor antibiotics produce their effect mainly by direct action on DNA, leading to disruption of the DNA function.
- All the anticancer antibiotics now being used in clinical practice are products of various strains of the soil microbe *Stremptomyces.*
- Cell cycle non-specific.
- **Agents:** Doxorubicin, daunorubicin, idarubcin.

هدول عبارة عن cell cycle nonspecific they just incorporated in DNA like alkylating agent

Deemah Sartawi