Anticancer Drugs
Part 3

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Pharmacology 3

Pyrimidine antagonists

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

5-Fluorouracil (5-FU)

Mechanism of action:

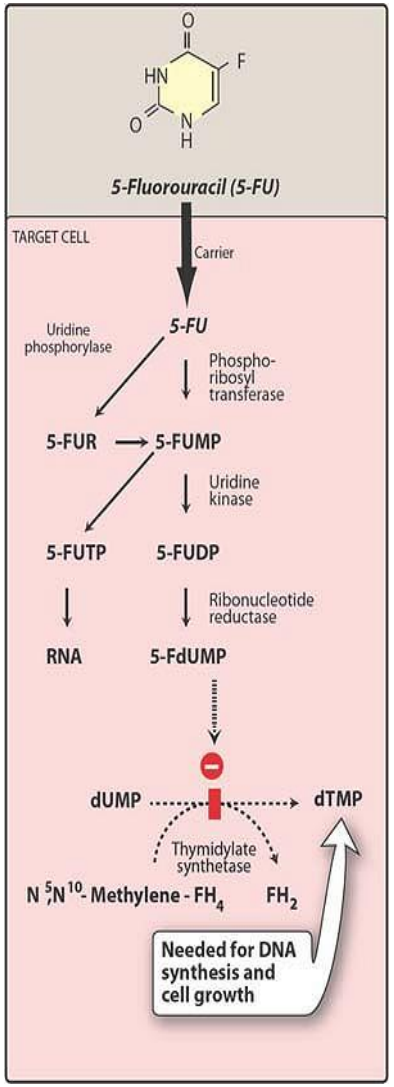
- 5-Fluorouracil (5-FU) is inactive in its parent form and requires activation via a complex series of enzymatic reactions to:

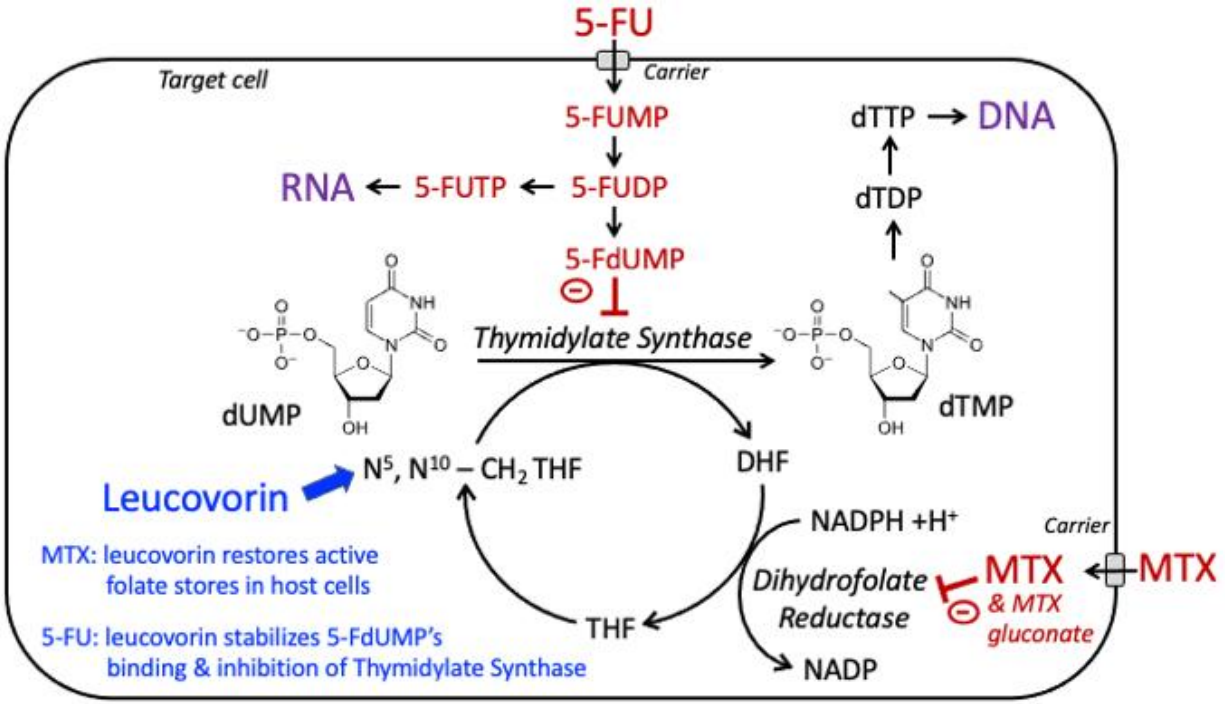
1. **FdUMP** which inhibits thymidylate synthase (TS)..Main mechanism

2. **FdUTP** which can be incorporated into cellular DNA, resulting in inhibition of DNA synthesis and function.

3. **FUTP** which is then incorporated into RNA, where it interferes with RNA processing and mRNA translation.

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





Mechanism of action of leucovorin to reverse or "rescue" the inhibitory effects of methotrexate (MTX) on thymidine synthesis, and intensify the effects of 5-fluorouracil (5-FU) on thymidylate synthase. DHF: dihydrofolate; THF: tetrahydrofolate; N^5,N^{10} - CH_2 THF:5,10-methylenetetrahydrofolate.

5-FU

Pharmacokinetics:

- Because of severe toxicity to the GI tract, 5-FU is administered IV or, in the case of certain types of skin cancer, topically.
- 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.
- 5-FU is rapidly metabolized in the liver, lung, and kidney.
- The dose of *5-FU* must be adjusted in impaired hepatic function.

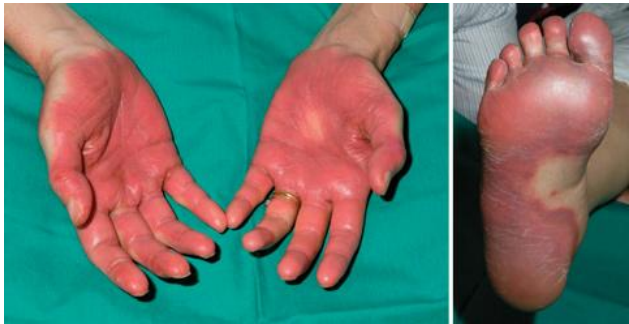
5-FU

Clinical uses:

- It is used in the treatment of slow-growing solid tumors (for example, colorectal, breast, ovarian, pancreatic, and gastric carcinomas).

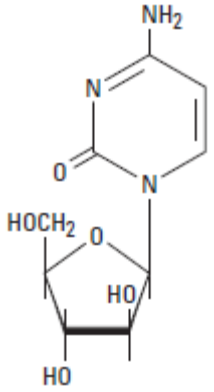
Side Effects:

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



Other pyrimidine antagonists

Cytarabine



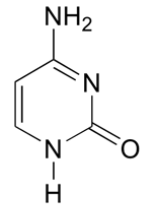
Cytosine arabinoside (cytarabine)

Mechanism of action:

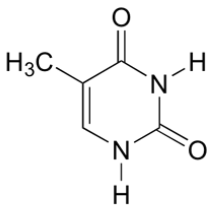
- **Cytarabine (ara-C)** like the other purine and pyrimidine antagonists, must be sequentially phosphorylated to the nucleotide.
- **Ara-CTP is the main cytotoxic metabolite**.
- Ara-CTP:

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 DNA. Incorporation into DNA leads to interference with chain elongation.

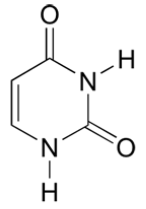
Other pyrimidine antagonists
Cytarabine



cytosine



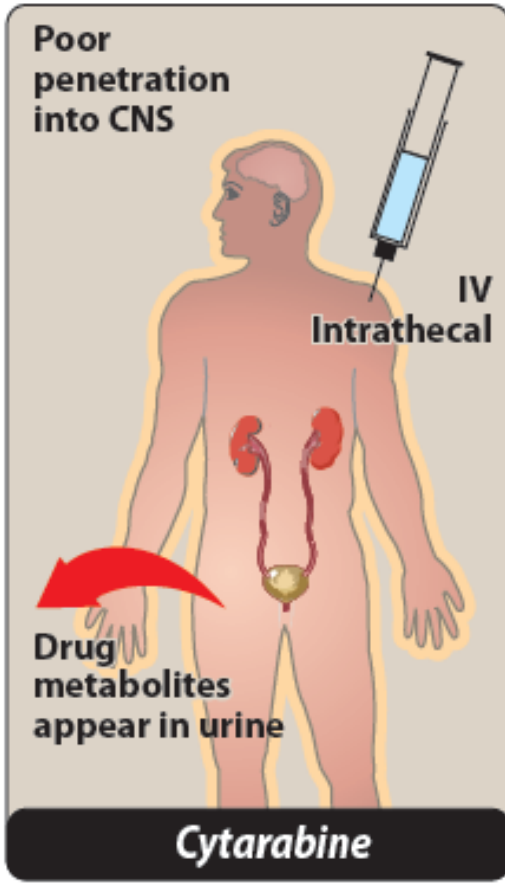
thymine



uracil

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. Therefore, 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.

Side Effects:

- Myelosuppression, mucositis, nausea and vomiting, and neurotoxicity when high-dose therapy is administered.

Other pyrimidine antagonists

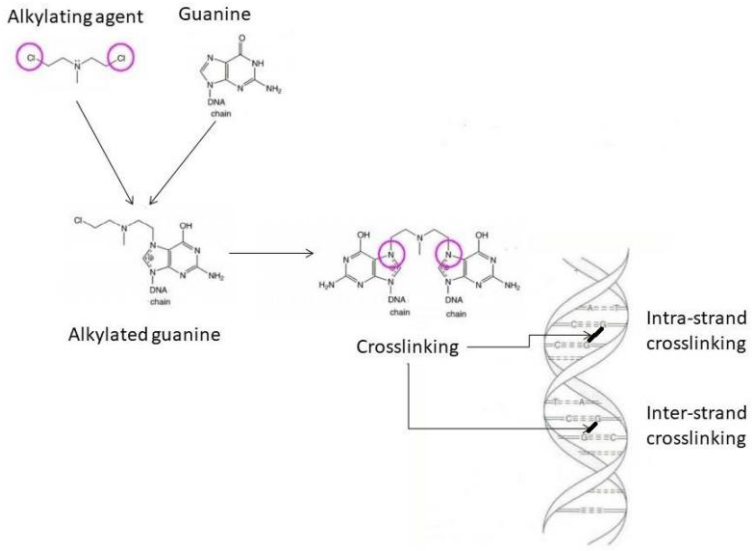
- **Capecitabine**
- **Gemcitabine**

Alkylating agents

1) **Nitrogen mustards:** chlorambucil, cyclophosphamide, mechlorethamine
2) **Nitrosureas:** carmistine, lomustine
3) **Alkylsulfonates:** busulfan
4) **Platinum analogs:** cisplatin, carboplatin, and oxaliplatin
5) **Other Alkylating Agents**: dacarbazine, procarbazine, & bendamustine

Alkylating agents

- **Mechanism of action:**
- Form reactive molecular species that transfer of their alkyl groups to various cellular constituents
- The macromolecular sites of alkylation damage include DNA, RNA, proteins, and various enzymes
- Alkylations of DNA within the nucleus represent the major interactions that lead to cell death



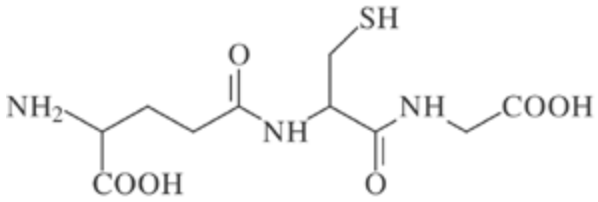
Alkylating agents

- **Are cell cycle-nonspecific**
- Primarily effective against rapidly proliferating cells.
- Used in combination with other agents to treat a wide variety of lymphatic and solid cancer.
- Are mutagenic and carcinogenic and can lead to secondary malignancies

Alkylating agents

- **Resistance:**
- The mechanism of acquired resistance to alkylating agents may involve:

1. Increased capability to repair DNA lesions through increased expression and activity of DNA repair enzymes.
2. Decreased transport of the alkylating drug into the cell
3. Increased expression or activity of glutathione and glutathione-associated proteins, which are needed to conjugate the alkylating agent, or increased glutathione *S*-transferase activity, which catalyzes the conjugation.

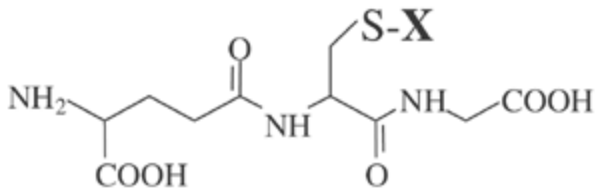


Glutathione

+

Xenobiotic (X)

GST



Glutathione-S-Conjugate

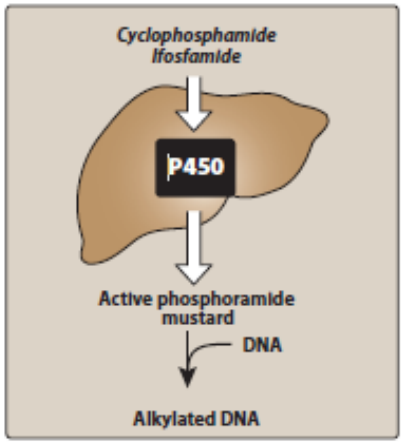
Cyclophosphamide

- Activated hepatically 4-hydroxyl cyclophosphamide.
- The hydroxylated intermediates then undergo breakdown to form the active compounds, phosphoramide mustard and acrolein.

Phosphoramide (active cytotoxic)

Acrolein (haemorrhagic cystitis)

- Haemorrhagic cystitis
  - Adequate hydration as well as IV injection of MESNA (sodium 2-mercaptoethane sulfonate), which neutralizes the toxic metabolites, minimizes this problem.]
- Other ADRs: Alopecia, NVD, Bone marrow suppression



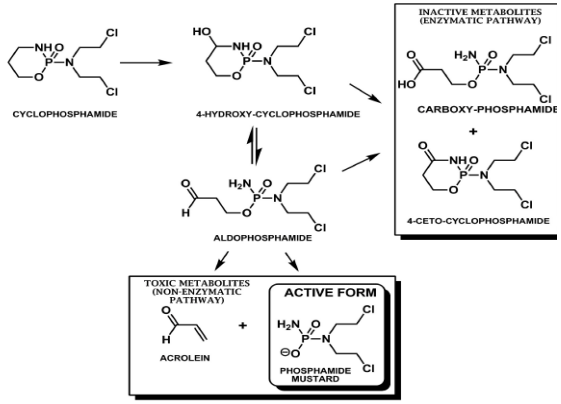
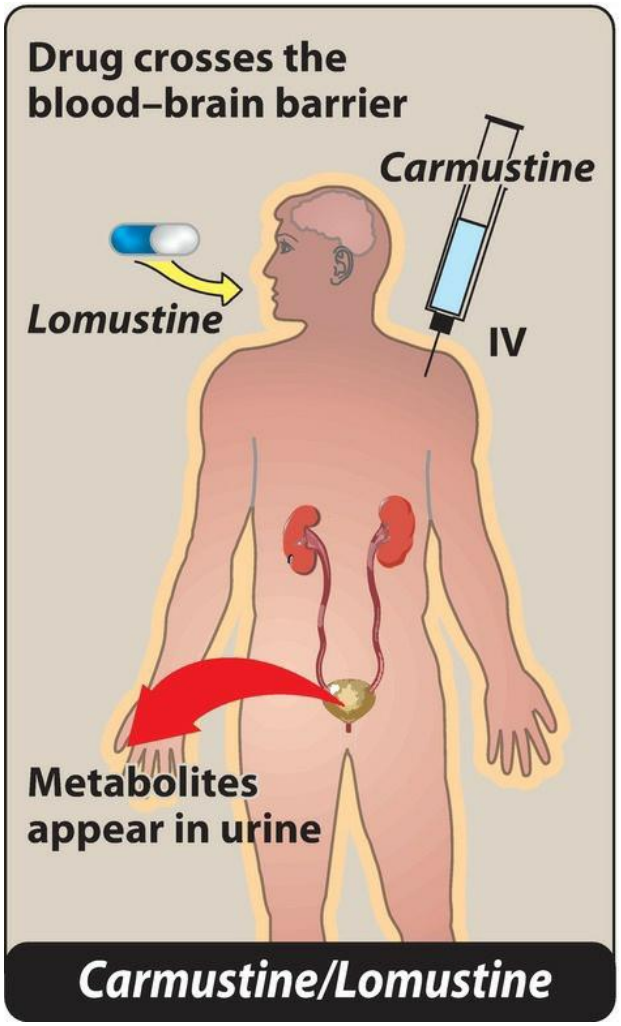


FIGURE 13 - Diagram of cyclophosphamide bioactivation.

Nitrosoureas

- **Carmustine** and **lomustine** are closely related nitrosoureas.
- Penetrate into the CNS and used for treatment of brain tumors.
- **Streptozocin** is another nitrosourea that is specifically toxic to the β cells of the islets of Langerhans, hence its use in the treatment of insulinomas.



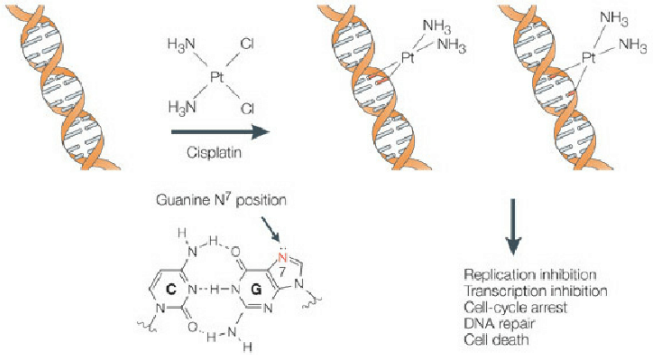
Adverse effects:

- Myelosuppression
- N/V
- Streptozotocin is also diabetogenic.

Platinum analogs

1) **First generation: Cisplatin**

- because of its severe toxicity, *carboplatin* was developed.



- ADEs:
- **Renal toxicity** (major) and can be prevented by aggressive hydration.
- **N and V** (may continue for as long as 5 days. Premedication with antiemetic agents is required).
- **Hearing loss** (10 to 30% of patients)
- **Neuropathy** (can include tingling in the extremities and numbness)

Platinum analogs

2) Second generation: **Carboplatin**

- MOA, mechanisms of resistance, and clinical uses are identical to cisplatin.
- *Carboplatin* is used when patients cannot be vigorously hydrated, as is required for *cisplatin* treatment or if they suffer from kidney dysfunction or are prone to neuro- or ototoxicity.
- it exhibits significantly less renal toxicity and gastrointestinal toxicity, peripheral nerves, and hearing loss.
- It is more myelosuppressive than cisplatin.

3) Third generation: **Oxaliplatin**

- Similar to cisplatin and carboplatin.
- ADEs: Neurotoxicity manifested by a peripheral sensory neuropathy

Questions??