Anticancer drugs 2

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3. Antibiotics for cancer therapy

inhibit DNA & RNA synthesis; they behave as both phase specific (Bleomycin) & phase non specific agents they include:

Dactinomycin, Daunarubicin, Doxorubicin Mitomycin, & Mitozantrones (Idarubicin & Aclarubicin).

The antibiotics depress BM, cause GIT upsets& stomatitis, Alopecia,

cardiomyopathy (Daunarubicin & Doxorubicin),

pulmonary fibrosis & skin rashes (Bleomycin).

Doxorubicin & Daunorubicin

Uses:

1. Doxorubicin breast CA, lymphomas, sarcomas, lung CA, stomach CA & thyroid CA.
2. Daunorubicin for Acute Myeloid Leukemia (AML).

Both drugs are given I.V., inactivated in GIT (not given orally) don't penetrate CNS, extensively metabolized & excreted mainly in bile.

4. Antimetabolites

These include:

1. A folic acid antagonist: Methotrexate (MTX).
2. Purine antagonists: mercaptopurine 6-MP, Azathioprine and thioguanine, Fludarabine, cladribine.
3. Pyrimidine antagonists: capecitabine, Fluorouracil (5FU), cytarabine,

Fludarabine: used in low grade non Hodgkin and CLL.

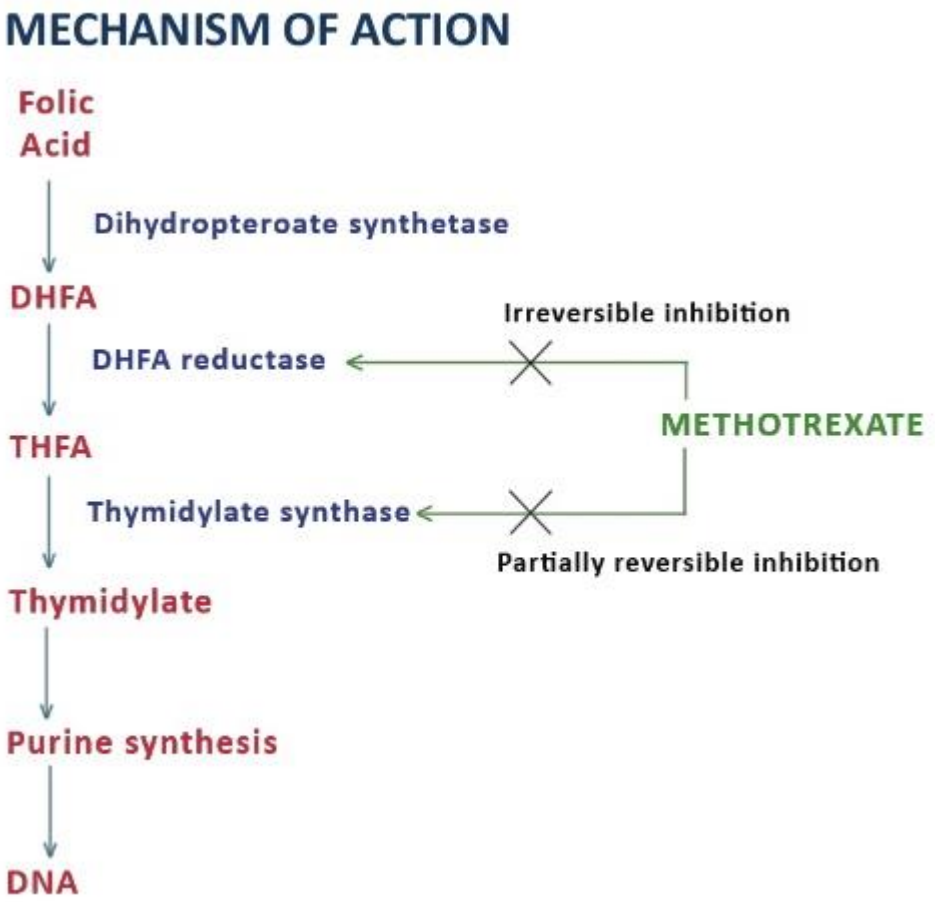
Cladribine: used as Fludarabine and in hairy cell leukemia

Adverse effect:

1. GIT upset (ulceration, mucositis).
2. B.M. depression.
3. Renal impairment potentiates their toxicity.

Methotrexate

- Mechanism of action: structurally related to folic acid,
- acts as folic acid antagonist by inhibiting (dihydrofolate reductase) which is responsible for conversion of folic acid into active form (tetrahydrofolic acid) which is important in synthesis of amino acids & nucleic acids.



- MTX can be inhibited by giving FOLINIC acid (leucovorin) & this is called "leucovorin rescue" which means B.M. rescue (from suppression)
- The consequences of ↓ FH 4 leads to ↓ biosynthesis of thymidilic acid, amino acids & purines → ↓ DNA, RNA synthesis, ↓ protein synthesis → cell death.

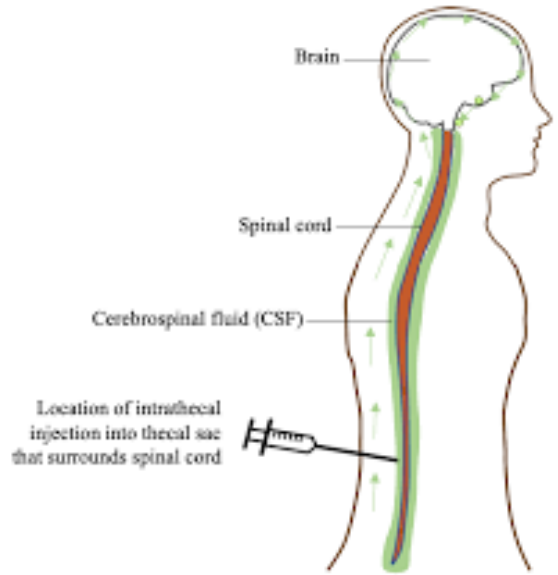
- Kinetics:

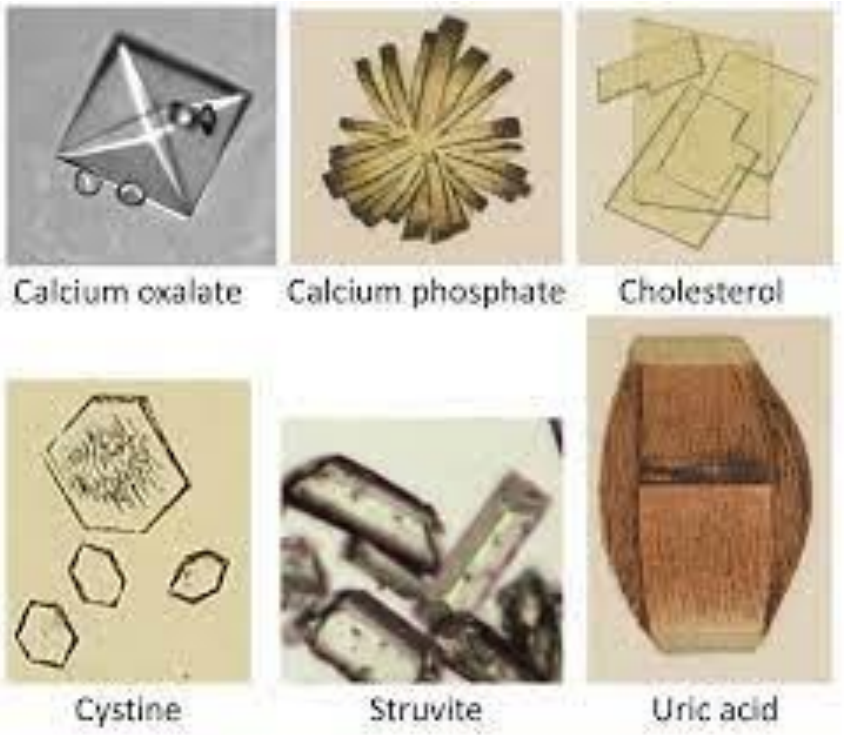
1. Rapidly absorbed from gut.

2. Given I.M., I.V., intrathecally because it poorly penetrates CSF.

3. MTX also undergoes hydroxylation (7-OH metabolites) both (MTX+ metabolites) are excreted in urine.

4. 7-OH metabolite has ↓ water solubility → crystalluria, therefore, good hydration & alkalinization of urine is important to avoid renal toxicity.





Adverse effects: stomatitis, B.M. suppression, alopecia, N & V , diarrhea, erythema, rash & urticaria.

Other toxicities: Renal, hepatic, pulmonary & neurologic toxicity (intrathecally → meningitis-like picture).

Contraindications : pregnancy because it causes abortion & it's teratogenic.

6-Mercaptopurine (6-MP)

It's a an analog of hypoxanthine. Azothioprine (an Immunosupp.) exerts its effects after conversion to 6-MP.

Mechanism of action (site of action): it penetrates target cells & is converted to Thio-IMP which inhibits purine synthesis.

Uses: for maintenance of remission in ALL (Acute Lymphoid Leukemia), absorption by oral route is weak, doesn't penetrate CNS.

Metabolized in the liver to thio uric acid by (Xanthine oxidase). Allopurinol (xanthine oxidase inhibitor) therefore; ↑ toxicity of 6-MP.

Adverse effects: N & V, diarrhea, B.M. depression, hepatotoxicity.

6-Thioguanine (6-TG)

Another purine analog, used primarily in Rx of Acute Non Lymphocytic Leukemia in combination with daunorubicine & cytarabine.

Like 6-MP it must be converted to the corresponding nucleotide from which will inhibit purine synthesis.

5-Fluorouracil (5-FU)

It's a pyrimidine analog. To be cytotoxic 5 FU is converted to (5-F dump) which competes for thymidylate synthetase (T.S.)

5-F dump acts as pseudo substrate entrapped with the enzyme that can't proceed to products. DNA synthesis ↓ because of thymidine lack. 5 FU is also incorporated in the RNA.

Uses: solid tumors, colorectal CA, breast & ovarian CA, pancreatic & gastric CA.

Adjuvant therapy with Levamisole improves survival of colon CA.

Adverse effects: severe toxicity to GIT if given orally, so taken I.V. Penetrates well to the CSF. Metabolized in the liver to CO_2 . Toxicity includes beside the GIT, BM depression & hand foot dermopathy.

Cytarabin (Ara-C)

A pyrimidine antagonist. It is S phase specific

Uses: AML (Acute Myeloid Leukemia) in combination with 6-TG & Daunorubicin.

Ara-C is ineffective orally, is given I.V., doesn't penetrate to the CSF (can be injected intrathecally).

Adverse effects: N & V, diarrhea, severe B.M., suppression hepatotoxicity.

Fludarabine

It's purine nucleotide, inhibits DNA and RNA synthesis

Uses: CLL (chronic Lymphoid Leukemia) may replace chlorambucil. Hairy cell leukemia. It's given I.V.

Miscellaneous

Procarbazine

Inhibits DNA & RNA synthesis. It is given orally & parenterally, penetrates the CSF, excreted in urine together with its metabolite.

Adverse effects: BM depression GIT & neurotoxicity. It inhibits MAO (contraindicated with Tyramine contained food) , it induces Disulfiram reaction with Alcohol. It's both mutagenic & teratogenic (cause non-Lymphocytic leukemia).

L-Asparaginase

It's derived from bacteria, it catalyses the deamination of Asparagine → Aspartic acid & ammonia. Neoplastic cells require an extra source of asparagine to support growth & function. The drug will hydrolyze blood Asparagine thus deprives tumor cells of their nutrient required for protein synthesis.

Uses: for ALL in combination with vincristine & prednisolone. It is given I.V. or I.M.

Toxicity: hypersensitivity reactions → ↓ clotting factors & liver abnormalities, also Pancreatitis, coma, seizures

Thank you